

<b>Fiscal Year:</b>	FY 2020	<b>Task Last Updated:</b>	FY 04/12/2020
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<b>Project Title:</b>	Proteomic Signatures of Space Radiation Induced Cardiovascular Degeneration		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>			
<b>Program/Discipline--Element/Subdiscipline:</b>	HUMAN RESEARCH--Radiation health		
<b>Joint Agency Name:</b>	<b>TechPort:</b>	No	
<b>Human Research Program Elements:</b>	(1) <b>SR:</b> Space Radiation		
<b>Human Research Program Risks:</b>	(1) <b>Cardiovascular:</b> Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
<b>Start Date:</b>	05/12/2016	<b>End Date:</b>	05/11/2022
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	
<b>No. of PhD Candidates:</b>	1	<b>No. of Master' Degrees:</b>	
<b>No. of Master's Candidates:</b>		<b>No. of Bachelor's Degrees:</b>	
<b>No. of Bachelor's Candidates:</b>		<b>Monitoring Center:</b>	NASA JSC
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<b>Flight Program:</b>			
<b>Flight Assignment:</b>	NOTE: End date changed to 5/11/2022 per L. Barnes-Moten/JSC and NSSC information (Ed., 5/10/21) NOTE: End date changed to 5/11/2021 per NSSC information (Ed., 8/12/20)		
<b>Key Personnel Changes/Previous PI:</b>			
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<b>Grant/Contract No.:</b>	NNX16AK20G		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

**Task Description:**

Radiation damage and the cell's attempt to repair it triggers a myriad of signal transduction pathways which alter gene, and ultimately, protein expression. Space radiation may affect biomolecules, cellular processes, and ultimately the cellular protein content (the proteome) differently than radiation present on Earth. Epidemiological analysis of terrestrial radiation exposure indicates that single high- or multiple low-dose radiation exposure can culminate in a wide array of cardiac injury and malfunction over time. Based on terrestrial data, it is believed that cardiovascular disorders may develop in astronauts from exposure to the space radiation environment. Indeed, a recent study by Yan et al. (2014), found that a single full body exposure to a low dose of proton or iron particle radiation, which somewhat mimics the space radiation environment, was sufficient to induce a significant, long term, negative effect on murine cardiovascular function. In this proposal, we take advantage of our expertise with bioinformatics analysis of cardiovascular proteomic data sets and murine cardiovascular physiology to evaluate the consequences of low dose, chronic space radiation, or mixed field space radiation on the dynamics of the cardiac proteome and to understand how the radiation induced changes relate to cardiovascular function. In doing so, we will extend Yan et al.'s work by identifying a proteomic signature that predicts the development of permanent cardiovascular degeneration from a single low dose space radiation exposure. Further, we seek to evaluate whether the proteomic signatures differ when mice experience repeated exposures of space-like radiation or mixed field space radiation. This information will lead to a mechanistic understanding of the altered cellular and molecular processes contributing to the development of cardiovascular dysfunction at the organ and organismal level in scenarios better mimicking the space radiation environment. This information is needed to predict, monitor, and prevent cardiac damage during long term space flight. Reference: Yan, X., et al., Cardiovascular risks associated with low dose ionizing particle radiation. PLoS One, 2014. 9(10): p. e110269.

**Rationale for HRP Directed Research:****Research Impact/Earth Benefits:**

Limited information is known regarding the impact of chronic low level radiation on cardiovascular molecular biology and function both terrestrially and during extended space exploration. Our research is expected to provide information in regards to terrestrial and astronaut health. Innovative technologies that may arise from our studies may include novel biomarkers predictive of cardiovascular susceptibility to chronic low level radiation as well as countermeasures that may be employed both on Earth as well as during space exploration.

The long-term objective of this study is to identify molecular mechanism(s) underlying space radiation induced cardiovascular dysfunction. Our hypothesis is that the onset and magnitude of cardiac dysfunction (phenome) can be predicted by cardiac proteomic signatures arising from injury produced by distinct space radiation exposures. To address this hypothesis, we will define the cardiac phenome-proteome after iron, oxygen, and gamma radiation exposure. Five month old male C57Bl6 mice (Jackson Laboratories) underwent transthoracic echocardiograms at Duke University Medical Center to establish baseline cardiac function. Subsequently, mice were subjected to single fully body irradiation at Brookhaven National Laboratories (BNL) under the following conditions: a) gamma (50-400cGy), b) 16O (15-150cGy/ 600 MeV/n), c) 56Fe (15-150cGy 1 GeV/n), d) Galactic Cosmic Radiation (GCR) (150cGy). All radiation groups included sham irradiated control animals. A subset of these animals underwent comprehensive cardiac structural and functional evaluation at 9-12 months post radiation including a) serial transthoracic echocardiograms capturing systolic and diastolic parameters, b) terminal pressure volume PV loop hemodynamic assessments, c) cardiac MRI, (d) blood pressure assessment, and e) cardiac and aortic tissue histology and immunohistochemistry. All echocardiograms were performed on awake animals, and were independently interpreted by two clinicians in a blinded fashion. Cardiac MRIs were performed using a 7.0 T Bruker Biospec small animal MRI scanner. Approximately 1000 mice were irradiated during five different BNL campaigns.

Non-invasive echocardiography and cardiac MRI did not demonstrate gross differences on systolic and diastolic function in GCR treated mice in comparison to controls. However, invasive pressure-volume loop hemodynamic analyses demonstrated that GCR treated mice, in comparison to controls, have a significant reduction in load independent (Preload Recrutable Stroke Work) and load dependent measures of cardiac systolic function (Cardiac Output and Stroke Volume). The differences in systolic function are partly explained by GCR induced increases in arterial elastance, suggesting that GCR exposure increases vascular resistance and afterload. The rise in afterload is associated with elastic fiber thickening, degeneration and disruption in aortic tissue, identified by histology that is present in GCR irradiated mice and absent in age-matched controls.

**Task Progress:**

Quantitative mass spectrometry was performed on peptides (total proteome) as well as phosphopeptides (phosphoproteome) obtained from digested protein homogenates from the hearts of male C57B6 mice that had undergone radiation exposure at the NASA Radiation Science Laboratory at Brookhaven National Laboratories. These mice were subjected to single fully body irradiation at 6 months of age under the following conditions: a) 56Fe (50 cGy; n=3; obtained 3 month post radiation), b) 16O (50 cGy 600 MeV/n; n=3; obtained 7 months post radiation), c) 56Fe (50 cGy 1 GeV/n; n=3; obtained 7 months post radiation), and d) GCR (150 cGy, n=6; obtained 8 months post radiation). All radiation groups included sham irradiated control animals. Bioinformatics analysis of mass spectrometry data sets include: a) identification of significantly expressed proteins for each dose and radiation types compared to corresponding control samples, (b) pathway enrichment analysis using functional annotation data obtained from Gene Ontology, KEGG (Kyoto Encyclopedia of Genes and Genomes), Reactome, and Molecular Signature Database (MSigDB), and c) identification of protein and pathway interaction modules that distinguish molecular signature of the various radiation types.

From the hearts of gamma, 56Fe, and 16O irradiated mice, 4,381 proteins and 5435 phosphopeptides were quantified. Similarly, from hearts from GCR irradiated mice, 4,650 proteins and 7,002 phosphopeptides (mapping to 303 phosphoproteins) were quantified. Pathways commonly influenced by all radiation types evaluated include mitochondrial gene expression and translation and fatty acid catabolic processes and oxidation. Pathways uniquely modulated by GCR involve cornification and keratinization.

Our data suggests that, in contrast to other forms of radiation, a single exposure to GCR increases afterload by injuring aortic architecture, and causes pronounced defects in load dependent cardiac systolic function. The cornification and keratinization processes observed in heart tissue from GCR irradiated animals may be contributing to the cardiovascular functional decline observed by hemodynamic and MRI analyses of these mice. Further characterization of the proteins involved in these processes may serve as targets of GCR countermeasures.

Bibliography Type:		Description: (Last Updated: 07/11/2023)
Articles in Peer-reviewed Journals		Brown ZD, Bishawi M, Roan J-N, Lee F, Nevo A, Watson M, Bowles DE. "The use of an inexpensive Processing Aid Device (the Mouse PAD) to facilitate rodent tissue banking." Biotechniques. 2020 Jul;69(1):364-8. Epub 2020 May 18. <a href="https://doi.org/10.2144/btn-2019-0069">https://doi.org/10.2144/btn-2019-0069</a> ; PMID: 32418443 , Jul-2020