Fiscal Year:	FY 2019	**Task Last Updated:**	FY 03/13/2019
PI Name:	Bowles, Dawn Ph.D.		
Project Title:	Proteomic Signatures of Space Radiation Induced Cardiovascular Degeneration		
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:	27710-0001	**Congressional District:**	4
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
Start Date:	05/12/2016	**End Date:**	05/11/2020
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Abraham, Dennis M.D. (Duke University) Kidane, Yared Ph.D. (Wyle Laboratories, Inc.) Mao, Lan M.D. (Duke University) Dewhirst, Mark D.V.M., Ph.D. (Duke University) Moseley, Martin Ph.D. (Duke University)		
Grant/Contract No.:	NNX16AK20G		
Performance Goal No.:			
Performance Goal Text:			

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 heath. 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.
Task Progress:	Five trips to Brookhaven National Laboratory (BNL) for mice experimentation have been made for this grant (Fall 2016, Spring 2017, Fall 2017, Summer 2018, and Fall 2018). For Fall 2016 studies 110 Male C57B6 mice were acquired from Jackson Laboratories. These mice were shipped to Duke University Medical Center where at 5 months of age they underwent transthoracic echocardiograms to establish baseline cardiac function. Parameters evaluated included (a) M-mode (done in both long and short axis), (b) Septal and posterior wall width in diastole, (c) End diastolic dimension and end systolic dimension, (d) aortic valve velocity, and (e) aortic ejection time (all measured and averaged over 3 consecutive beats). Echocardiogram images were also acquired for measurement of diastolic dysfunction and strain. Mice were shipped to the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratories where they were subjected to single full body irradiation at 6 months of age under the following conditions: a) gamma (50cGy, 100cGy, 200cGy), b) 16O (15cGy, 25cGy, 50cGy/ 600 MeV/n), c) 56Fe (15cGy, 25cGy, 50cGy 1 GeV/n). There were a total of 20 sham irradiated control animals who traveled to NSRL. Evaluations include: a) serial transthoracic echocardiograms capturing all above parameters, b) terminal pressure volume loop hemodynamic assessments. Overall conclusions from the Fall 2016 experiment were that no significant changes in any echo measurement at any dose or rad type compared to control at any time point were observed. However across all groups including controls aging related decrements in function were observed as expected. Caveats were that this was essentially a pilot study (n=10 per group). There was also excessive early fighting among mice. The study was terminated at 9M post rad with the exception of a small group of animals which were held to 1 year post radiation when pressure volume (PV) loops were obtained. There was no significant difference in invasive hemodynamic measurements at 1 year post radiation. Again, small # of animals was examined in this manner. A larger group of mice were evaluated in Spring 2018. Energies and doses are the following: Gamma (50cGy, 100cGy, 200cGy), 16Ox 600 MeV/n (15cGy, 25cGy, 50cGy), 56Fe 1GeV/n (15cGy, 25cGy, 50cGy). There was a larger number of animals per group in this experiment. Echocardiographic images have been obtained for each of the animals (if they were alive at the time of Echo acquisition) at the following time points: Pre-irradiation, 1 week post, 1M post, 2M post, 3M post, 4M post, 7M post, 9M post. Pressure volume (PV) loops were acquired on 30 animals 9 M post radiation. At the time of experiment termination, multiple organs were processed and biobanked for 'omics analyses and future collaboration. Overall, the echo reads for Spring 2017 are ongoing. We had a computer hard drive malfunction and lost a large amount of analyzed data. Therefore, no definite conclusions can be made yet with this larger cohort of animals. The PV loop analysis focused on 56Fe 50cGy, 1 year post IR with 10-15 per group. No statistically significant differences were observed in these measurements. However, a trend in several measurements was observed which suggests the possibility of diastolic dysfunction development. Additional PV loops have been done from animals in Fall 2017 experiment but have yet to be analyzed. Between Fall 2016 and Spring 2017 experiments we have developed an extensive biorepository of tissues for molecular analyses and for collaborations. For the NSRL Fall 2017 experiment the same energies and doses from the two previous experiments were used. Echocardiographic images have been obtained for each of the animals at the following time points: Pre-irradiation, 1M post, 2M post, 3M post, 4M post, 7M post, 9M post, 16M post. PV loops were acquired on 97 animals 16M post radiation. All of these echos and PV loops are yet to be analyzed. At the time of animal sacrifice, multiple organs were processed and biobanked for 'omics analyses and future collaboration. A subset of animals were AHA labeled for mass spec proteomics analyses. Brain regions from a subset of animals (59) were processed by Andrew Wryobek for funded tissue sharing FLAGSHIP grant in March 2019. NSRL Summer 2018 study examined GCR (galactic comic radiation) sim 5 ion (150 cGy). Echocardiographic images have been obtained for each of the animals at the following time points: Pre-irradiation, 1M post, 3M post, 7M post, 8M post. Echos are planned for 11 and 17M post irradiation in May 2019 and Nov 2019, respectively. PV loops are planned for November 2019. 12 animals have been labeled with AHA and submitted to Duke Proteomics Core for dynamic, abundance, and phosphoproteomics analyses. Echos are currently being read for this cohort. Data is still preliminary. Outline of the study design for the Group 5 mice irradiated at NSRL Fall 2018. Energies and doses are the following:

	Gamma (300cGy, 400cGy), 16Ox (75cGy, 150cGy) 600 MeV/n, 56Fe (75cGy, 150cGy) 1 GeV/n, GCR sim 5 ion (150 cGy). Echocardiographic images have been obtained for each of the animals (if they were alive at the time of Echo acquisition) at the following time points: Pre-irradiation, 2M post, 3M post, 4M post. Echos are planned 7M, 9M, 12M, and 18M post irradiation. PV loops are planned for May 2019.
Bibliography Type:	Description: (Last Updated: 03/11/2025)
Articles in Peer-reviewed Journals	Brown ZD, Bishawi M, Bowles DE. "Using proteomics approaches to understand mechanisms underlying low LET or GCR radiation-induced cardiovascular disease." THREE. 2018 May 15. https://three.jsc.nasa.gov/articles/Proteomics_Bowles.pdf , May-2018