Fiscal Year:	FY 2023	**Task Last Updated:**	FY 03/19/2023
PI Name:	Tahimic, Candice Ginn Ph.D.		
Project Title:	Cardiovascular Responses to Simulated Spaceflight: Molecular Signatures and Surrogate Outputs to Measure CVD Risk		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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 (2) **Immune**:Risk of Adverse Health Event Due to Altered Immune Response		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2019 HERO 80JSC019N0001-FLAGSHIP & OMNIBUS: Human Research Program Crew Health. Appendix A&B
Start Date:	01/28/2021	**End Date:**	03/31/2023
No. of Post Docs:	0	**No. of PhD Degrees:**	
No. of PhD Candidates:	0	**No. of Master' Degrees:**	
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	7
No. of Bachelor's Candidates:	7	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 03/31/2023 per NSSC information (Ed., 5/18/23).		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Goukassian, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai) Ronca, April Ph.D. (NASA Ames Research Center)		
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Performance Goal No.:			
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Task Description:	In this ground-based rodent study, we aim to systematically define molecular signatures of cardiovascular performance across doses of acute simulated galactic cosmic radiation (Five-ion GCR) at early and late timepoints post-exposure. We also will determine the contribution of biological sex and the combined effects of GCR and microgravity on clinically relevant and emerging measures of cardiovascular health. We hypothesize that exposure to space radiation alone or in combination with microgravity results in early and late changes in the structure, transcriptome, redox signaling, and cytokine milieu of cardiovascular tissue, some of which have known links to decreased performance, aging, and increased cardiovascular disease (CVD) risk. We further posit that other less invasive clinically relevant measures of immune, behavior, and neuromotor function will be informative towards extrapolating the effects of deep space missions on human cardiovascular health. To achieve the project goals and test the hypothesis, we will take advantage of a rare tissue sharing opportunity from a recently funded Human Research Program (HRP) study. The experiment design of this funded investigation includes a GCR dosing study on crew age-matched female and male mice (6 months old) as well as combined exposure study with simulated microgravity. A comprehensive panel of outcomes will be assessed in the funded study and includes measures of immune health, brain molecular and structural changes, behavior, anxiety, cognition, and neuromotor function. Our proposed approach is to measure clinically relevant indicators of cardiovascular performance and perform transcriptomic profiling by RNAseq to determine dose and time-dependency of cardiovascular responses. To further facilitate extrapolation of results to humans, rodent RNAseq data will be compared to publicly available human RNAseq datasets from aging and CVD progression studies. The results from analysis of rodent cardiovascular tissue also will be compared to corresponding blood data to link immune and cardiovascular changes. Further, cardiovascular findings will be interpreted in light of behavioral testing results to gain insight on any relationships between cardiovascular outcomes and changes in neuromotor, anxiety levels, and cognitive performance. The significance/impact of this study is that it contributes to increased understanding on the mechanisms of degenerative changes in cardiovascular tissue and the clinical endpoints they suggest. This study also is expected to provide insight on the latency period for radiation-induced cardiovascular changes and any sex differences in these outcomes. Lastly, our findings are expected to generate testable hypotheses for the development of countermeasures and less invasive surrogate biomarkers to monitor cardiovascular health in-flight and after return.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This study is expected to contribute to increased understanding on the mechanisms of spaceflight-induced degenerative changes in cardiovascular tissue and the clinical endpoints they suggest. This study also is expected to provide insight on the latency period for radiation-induced cardiovascular changes and any sex differences in these outcomes. Lastly, our findings are expected to generate testable hypotheses for the development of countermeasures and less invasive surrogate biomarkers to monitor cardiovascular health in-flight and after return. Cardiovascular deconditioning observed in spaceflight resemble aspects of cardiovascular aging and disease on Earth. Hence, this study also may prove informative in the development new therapies for cardiovascular disease on Earth.
Task Progress:	Spaceflight leads to cardiovascular deconditioning in the absence of mitigation strategies. Cardiovascular changes in response to spaceflight are attributed to altered microgravity levels and the ensuing cephalad fluid shift. Overall reductions in physical activity and other factors – such as nutritional changes, elevated CO2 levels, and a demanding workload – also may be contributing factors. Although the literature is mixed, some of the reported cardiovascular changes associated with exposure to the spaceflight environment include reductions in left ventricular mass, transient atrial distension and heart rhythm disturbances. Orthostatic intolerance and stiffer carotid arteries also have been observed in spaceflight crew upon return to Earth. Changes in venous blood flow and thrombus formation also are potential risks of spaceflight. During deep space explorations, humans will be exposed to even longer periods of microgravity and higher doses of space radiation relative to International Space Station (ISS) missions. The development of effective countermeasures for deep space missions requires an understanding of the anticipated spectrum of cardiovascular outcomes. Human studies as described above have shed light on how the cardiovascular system responds to microgravity (and other current environmental stressors in low Earth orbit). However, there is limited information on whether cardiovascular responses to deep space radiation alone will be similar to the effects of microgravity or in combination. Therefore, in this investigation, we aimed to (1) determine radiation dose and time-dependence on measures of cardiovascular health in crew age-matched female and male mice using simulated space radiation, (2) determine the effects of simulated space radiation singly and in combination with simulated microgravity by hindlimb unloading (HU), and (3) determine whether cardiovascular changes induced by simulated space exposure or in combination with HU correlate with specific and measurable behavioral, neuromotor, and immune outcomes. The sex dependence of the responses to simulated spaceflight factors also was assessed. Our central hypothesis is that exposure to simulated space radiation results in long-term changes to the transcriptome, redox signaling, and cytokine milieu of cardiovascular tissue, some of which have known links to aging and increased cardiovascular disease (CVD) risk. We hypothesize that exposure to simulated space radiation, in combination with simulated microgravity exacerbates cardiovascular deficits compared to single factor exposure. In our first study, female and male C57BL/6J mice (23-24 week old) were exposed to a single dose of 5, 15, and 50 cGy of 5-ion galactic cosmic radiation (GCR) or sham-treated (0 cGy). Tissues were collected at 14 days and 124 days post-GCR. In a second study, mice underwent one week of simulated microgravity by hindlimb unloading (HU) and then exposed to a single dose of 15 cGy GCR. HU was conducted for an additional two weeks post-GCR exposure. Single factor exposure groups (HU or GCR only) also were included in the study. Tissues were collected after 21 days of HU (14 days post-GCR exposure). Collectively, our findings show long-term changes in the heart transcriptome after GCR exposure. Some of these genes are linked to the development of cardiovascular disease. A mixture of cardioprotective and CVD-associated transcriptional changes were observed. Proteins levels of a subset of CVD-relevant cytokines show sex differences, but no GCR nor HU effects. In aorta, markers for aging and mitochondrial health showed both sex and age effects. Our findings highlight the importance of sex-specific strategies in monitoring and maintaining cardiovascular health during and after deep space missions.
Bibliography Type:	Description: (Last Updated:)