Fiscal Year:	FY 2020	**Task Last Updated:**	FY 05/24/2020
PI Name:	Lemere, Cynthia Ph.D.		
Project Title:	Sex- and Apo E-specific Late CNS and Cardiovascular Effects of Space Radiation		
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) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **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:	02115-6110	**Congressional District:**	7
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2016-2017 HERO NNJ16ZSA001N-SRHHC. Appendix E: Space Radiobiology and Human Health Countermeasures Topics
Start Date:	06/01/2018	**End Date:**	05/31/2022
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	1
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:	May 2020 report: Dr. Doris Taylor, a Co-Investigator on this grant, recently left Texas Heart Institute (THI). She has appointed Dr. Camila Hochman Mendez of THI as the interim Co-Investigator until Dr. Taylor finds a new research home. The switch has been approved by THI and Brigham & Women's Hospital (BWH) Research Administration.		
COI Name (Institution):	Taylor, Doris Ph.D. (Texas Heart Institute) Hochman Mendez, Camila Ph.D. (Texas Heart Institute)		
Grant/Contract No.:	80NSSC18K0810		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Our overall objective is to determine the short- and long-term risks of radiation from the space environment on cognition, motor abilities, fatigue resistance, anxiety, and changes in the brain and cardiovascular system. In our first grant period, we determined that low-dose 56Fe (iron) radiation had long-term, sex-specific consequences on cognition, locomotion, neuroinflammation, and Alzheimer's disease (AD) pathogenesis, with males being more vulnerable than females. Analysis of proton-irradiated mice showed some overlapping yet some opposing effects compared to iron. We have developed a collaboration with Drs. Doris Taylor and Camila Hochman Mendez (Texas Heart Institute), Co-Investigators on this proposal, by sharing the heart, one kidney, and bone marrow from each of the mice irradiated in three of our studies. During the current grant period, we will extend our research by comparing our existing data from our current studies on the late central nervous system (CNS) and cardiovascular (CV) effects of a single dose of iron radiation or a single dose of protons with a single dose of 5-ion, mixed beam simulated galactic cosmic radiation (GCRsim) in male and female AD-like transgenic and wildtype mice, and gamma irradiated wildtype mice (Aim 1). In addition, we will examine the sex- and Apo E-specific late CNS and CV dose-specific effects of iron radiation in a novel AD-like mouse model modified by targeted replacement of murine Apo E with human Apo E3 or E4 to determine if human ApoE4, a strong risk factor for AD and CV disease, exacerbates the effects of radiation (Aim 2). This work will be conducted in collaboration with investigators at Wash U, Duke U, the RIKEN Brain Institute, and NYU (New York University). We will perform longitudinal Magnetic Resonance Imaging (MRI) on the brain and heart in a subset of mice in Aims 1 and 2 to determine radiation-induced changes within individual animals. In addition, mice will undergo extensive behavioral testing as well as pathological and biochemical analysis of brain and heart. Lastly, we will conduct a study to test 2 novel human 3D neural models of Alzheimer's disease, developed by our collaborators at Massachusetts General Hospital (MGH) and Massachusetts Institute of Technology (MIT) (Aim 3), for acute and late CNS effects of space radiation on neuronal health, amyloid plaques, tau pathology, and epigenetics, and to investigate the potential of these models for screening mitigating treatments in the future. In collaboration with Drs. Taylor and Hochman Mendez, we will also irradiate undifferentiated induced pluripotent stem cells (iPSCs) from human males and females to determine whether highly charged, high energy (HZE) particle irradiation alters their ability to differentiate into cardiomyocytes, morphology, and/or maturation. In summary, we propose to take our current studies to the next logical step in an effort to better understand the potential risks of galactic cosmic radiation (GCR) to the brain and cardiovascular system in order to prepare astronauts for long-term deep space mission, including missions to the moon and Mars.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The overall goal of our research is to better assess the central nervous system and cardiovascular risks to astronauts during and after deep space travel. To properly understand these risks in the diverse human population, we must account for how sex and genetic differences change the way radiation damage manifests. Our work characterizing these radiation-disease models will also create platforms for testing strategies for mitigating radiation damage to improve the safety and long-term health of the astronauts.
Task Progress:	During the first 4 years of our NASA-funded program, we determined that mice exposed to relatively small doses of single components of space radiation (iron nuclei or protons) resulted in changes in behavior, cognition, and brain health. These changes were dependent on the sex and underlying genetic disease susceptibility of the mice as well as on the specific dose received. Interestingly, we found that young adult female mice were more resistant than male mice to the effects of space radiation on cognition and Alzheimer's disease-like damage. Our collaborator, Dr. Doris Taylor (Texas Heart Institute), found similar dependencies of radiation-induced changes in heart and kidney tissues from these same mice. In our current successor grant, we are extending these studies to examine the effects of a mixed-ion simulation of space-like radiation, known as "simulated Galactic Cosmic Radiation" (GCRsim) at doses predicted for astronauts traveling on long-term missions into deep space. Our current mouse studies (Aims 1 and 2) examine how sex differences and multiple genetic risk factors for Alzheimer's disease modify GCRsim radiation-induced changes in behavior, cognition, disease progression, brain and heart structure, and inflammation in the brain, heart, and kidney. Aim 1 builds upon our previous single-ion (iron and proton) studies but uses space-like mixed 5-ion GCRsim radiation exposure in the same Alzheimer's mouse model and wildtype mice. Aim 2 investigates the effects of a strong vascular Alzheimer's risk factor Apolipoprotein E4 in the same Alzheimer's mouse model and wildtype mice in response to GCRsim radiation. Equal numbers of female and male mice are included in each study. Due to the large number of mice required to achieve a statistically significant result, we have divided each of the mouse studies into two staggered cohorts to facilitate breeding, experimentation, and analyses. We use a 10-test behavioral battery that we developed during our first 4 years of funding to evaluate locomotion, strength, fatigue resistance, motor coordination, sensorimotor effects, psychological state, learning, and memory in mice. In addition, we utilize several novel human brain cell cultures (Aim 3), derived from immortalized progenitor neural cells and induced pluripotent stem cells (iPSCs) differentiated to neurons and glia, to investigate how space-like radiation affects human brain health in the context of specific disease-associated genetic factors. Our collaborators, Dr. Taylor and Dr. Camila Hochman Mendez (THI), are exploring the effects of space-like radiation on the heart and kidneys of our mice from Aims 1 and 2, as well as assessing GCRsim effects on heart cell function and maturation from irradiated iPSCs in Aim 3. All experiments include additional mice or cell cultures exposed to gamma radiation for comparison with those exposed to the space-like GCRSsim radiation. This aids us in interpreting our findings to understand radiation risk to humans. These studies involve strong collaborations with researchers at the Texas Heart Institute, Massachusetts General Hospital, Massachusetts Institute of Technology, Brookhaven National Laboratory, Duke University, Washington University School of Medicine, NYU School of Medicine, the RIKEN Brain Institute in Japan, the Harvard School of Medicine Mouse Behavior Core, and the Brigham & Women's Hospital Department of Radiology. To date, we have performed 2 in vivo radiation studies in mice for Aim 1. We bred and aged two identical cohorts of 114 mice, including female and male Alzheimer's-like mice and wildtype (WT) mice, staggered ~5-6 months apart. Aim 1A mice underwent pre-irradiation (IRR) MRI scans of brain and heart at 3.5 months of age, were transported to BNL for irradiationin April 2019, and were returned to BWH where they later underwent behavioral imaging and post-IRR MRI scans prior to sacrifice and tissue harvest at 12 months of age in December 2019. A total of 22 mice died prior to the end of the study, with female Alzheimer's mice having the highest attrition rate. The brains, hearts, and kidneys of the remaining 92 mice are currently undergoing analyses. Thus far, the preliminary data analysis of our behavioral studies from the first of two cohorts (and combining sexes) has revealed only a few effects of radiation. Locomotion was unaltered by GCRsim or gamma radiation. AD-like mice irradiated with 0.75 Gy GCRsim appeared to be less anxious whereas WT mice exposed to 2 Gy gamma radiation showed a tendency to be more anxious than non-irradiated mice. GCRsim irradiation had no effect on grip strength but 0.75 Gy gamma irradiation reduced grip

	strength in WT mice. Radiation, in general, had no effect on fatigue resistance but WT mice irradiated with 0.5 Gy GCRsim showed a hint of reduced fatigue resistance in one measure. WT mice that were irradiated with 0.75 Gy GCRsim had deficits in spatial memory, whereas gamma radiation had no effect. Depressive-like behaviors were not altered by radiation. As expected, brain levels of the Alzheimer's protein Ab42 were higher in female than male 12 month-old Alzheimer's-like mice, as previously demonstrated; however, no radiation-specific effects were observed. Cardiac MRI analysis revealed no genotype or radiation effects on heart structure or function. Heart and kidney tissues are being examined for radiation-induced changes gene expression and proteins related to fibrosis, inflammation, and cardiovascular function. Brain MRI analysis is ongoing. Pathological analyses will begin upon re-opening of the lab following the COVID-19 shutdown. Aim 1B mice, identical to Aim 1A, underwent pre-IRR MRI scans of brain and heart and irradiation at BNL in Oct 2019. These mice will undergo behavioral testing and post-IRR MRI scans at BWH in June 2020, followed by sacrifice and tissue harvest. For Aim 2, we have obtained approval and breeding pairs of the specific type of mice needed to assess the role of the Apo E4 in a novel Alzheimer's-like mouse model in the radiation response. Breeding is now underway. We will breed 2 staggered cohorts, similar to Aim 1 and expect to irradiate the first cohort of Aim 2 mice with GCRsim at BNL in Spring 2021. Equal numbers of female and male mice will be included. Regarding our cell culture experiments of Aim 3, we have completed a pilot irradiation study (May 2018) and two full irradiation studies (Nov 2018 and Apr 2019) at BNL using human neural cultures derived from immortalized progenitor cells that have been induced with Alzheimer's disease-associated mutations. We demonstrated the feasibility of transporting these cultures between Boston and Long Island with the pilot study and have collected data on how radiation affects disease progression with the full experiment. So far, we have found that a single 2 Gy dose of gamma radiation consistently increased Ab levels 1 week and 6 weeks post-IRR, whereas GCRsim had no effect in human neural cultures bearing Alzheimer's disease-associated mutations. We also ran a pilot study at BNL in Oct 2019 in which upon return, we plated human microglia immune cells on top of irradiated and non-irradiated human neural cells. We are currently optimizing the protocol for a future study later this year. We are also preparing for the first of the iPSC model experiments to compare the effects of GCRsim and gamma radiation in human iPSC-derived brain cells with different forms of Apolipoprotein E, including Apo E4, a major risk factor of Alzheimer's disease. We hope to run this experiment at BNL in the Fall 2020 campaign.
Bibliography Type:	Description: (Last Updated: 11/20/2024)
Abstracts for Journals and Proceedings	Hinshaw RG, Sowa MB, Park J, Kim DY, Ranzi RE, Hada M, Lemere CA. "Exposure of in vitro Brain Cells to Simulated Space Radiation." Presented at the 16th International Congress of Radiation Research (ICRR), Manchester, UK, August 25-29, 2019. Abstracts. 6th International Congress of Radiation Research (ICRR), Manchester, UK, August 25-29, 2019. , Aug-2019