Fiscal Year:	FY 2019	**Task Last Updated:**	FY 04/18/2019
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:**	
No. of Master's Candidates:	1	**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):	Taylor, Doris 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. Over the past 3 years, we have determined that low-dose 56Fe (iron) radiation has 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 is underway. Over the past year, we have developed a collaboration with Dr. Doris Taylor (Texas Heart Institute), Co-Investigator on this proposal, by sharing the heart, one kidney, and bone marrow from each of the mice irradiated in three of our studies. Over the next 4 years, 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 oxygen-16 or mixed beam galactic cosmic radiation (GCR) (protons, oxygen-16, and iron) 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 the same 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, and NYU. 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 organoid 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 Dr. Taylor, 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 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:	Over the past 4 years, we have demonstrated that, when mice are exposed to relatively small doses of single components of space radiation (iron nuclei or protons), the resulting changes in behavior, cognition, and brain health depend 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 are 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-component simulation of space radiation at doses predicted for astronauts traveling on long-term missions into deep space. Our current mouse studies (Aims 1 and 2) will examine how sex differences and multiple genetic risk factors for cardiovascular and Alzheimer's disease modify radiation-induced changes in behavior, cognition, disease progression, brain and heart structure, and inflammation in the brain, heart, and kidney. We will continue to use an 11-test behavioral battery that we developed during our first 4 years of funding to evaluate general health, strength, fatigue resistance, motor coordination, sensorimotor effects, psychological state, learning, and memory in mice. In addition, we will utilize several novel human brain cell cultures (Aim 3), derived from immortalized progenitor cells and induced pluripotent stem cells (iPSCs), to investigate how space-like radiation affects human brain health in the context of specific disease-associated genetic factors. Dr. Taylor's lab will assess the effects of this radiation on heart cell function and development from irradiated iPSCs. All experiments will include additional mice or cell cultures exposed to gamma radiation for comparison with those exposed to the space-like radiation. This will aid us in interpreting our findings to understand radiation risk in humans. These studies involve strong collaborations with researchers at the Texas Heart Institute, Massachusetts General Hospital, Massachusetts Institute of Technology, Brookhaven National Laboratory (BNL), Duke University, Washington University School of Medicine, NYC School of Medicine, the Harvard School of Medicine Mouse Behavior Lab, and the Brigham & Women's Hospital Department of Radiology. Thus far, we have prepared mice for the first of our radiation experiments at BNL and are currently performing pre-irradiation imaging of their brains and hearts. We have also completed requirements for obtaining the specific type of mice needed to assess the role of the Apo E allele in the radiation response in the second half of our mouse experiments. Regarding the cell culture experiments, we have completed a pilot irradiation (Spring 2018 campaign) and the first full irradiation (Fall 2018 campaign) at BNL with the human neural cultures derived from immortalized progenitor cells that have been induced with Alzheimer's disease-associated mutations. We have demonstrated the feasibility of transporting these cultures between Boston and Long Island with the pilot study and have collected initial data on how radiation affects disease progression with the full experiment. So far, we have found that non-mutant cultures show a radiation-induced reduction in a specific type of neuronal structural protein that accumulates in Alzheimer's disease whereas the mutant cultures did not show this reduction, and we are continuing to collect more data. We are currently growing cultures for the second full irradiation experiment in which we will let the cultures grow longer after irradiation before analyzing them and expect to detect stronger differences in Alzheimer's disease brain changes. In addition, we will examine the response of brain immune cells to irradiated neural cells in the Fall 2019 campaign. We are also preparing for the first of the iPSC model experiments in the Spring 2020 campaign.
Bibliography Type:	Description: (Last Updated: 11/20/2024)

Abstracts for Journals and Proceedings	Hinshaw RG, Sowa MB, Park J, Kim DY, Tanzi RE, Hada M, Lemere CA. "In vitro Neural Health After Simulated Galactic Cosmic Ray Exposure: A Pilot Study." 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. , Nov-2018
Abstracts for Journals and Proceedings	Hinshaw RG, Sowa MB, Park J, Kim DY, Tanzi RE, Hada M, Guida P, Lemere CA. "In vitro Exposure of Brain Cells with Simulated Galactic Cosmic Rays." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019
Abstracts for Journals and Proceedings	Lemere CA, Hinshaw RG. "Sex- and Apo E-Specific Late CNS and Cardiovascular Effects of Mixed Beam Galactic Cosmic Radiation: A Preview of Upcoming Studies." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019