Fiscal Year:	FY 2021	**Task Last Updated:**	FY 06/05/2021
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:		**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
Contact Monitor:	Zawaski, Janice	**Contact Phone:**	
Contact Email:	janice.zawaski@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	June 2021: As reported last year, 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, and the RIKEN Brain Institute. 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. Heart and kidneys will be examined by our THI collaborators. 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 differentiated induced pluripotent stem cell (iPSCs)-derived cardiomyocytes and endothelial cells from human males and females to determine whether GCRsim or gamma irradiation alters their gene expression, morphology or function. 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.
	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. Here, 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. GCRsim includes a mix of protons, silicon, helium, oxygen and iron ions. 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 tests low-dose space-like mixed 5-ion GCRsim radiation exposure in the same Alzheimer's amyloid mouse model and wildtype mice. Aim 2 investigates the effects of a strong vascular Alzheimer's risk factor Apolipoprotein E4 in another, more physiologically relevant Alzheimer's "knock-in" mouse model and wildtype mice in response to low-dose 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 perform pre-irradiation and post-irradiation MRI scans of the brain and heart in a subset of mice. The rest of the mice undergo a 10-test behavioral battery that we developed during our first 4 years of funding to evaluate locomotion, strength, fatigue resistance (endurance), 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 (Texas Heart Institute, 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 iPSC-derived cardiomyocytes and endothelial cells in Aim 3. All experiments include additional mice or cell cultures exposed to gamma radiation (similar to x-rays) for comparison with those exposed to the space-like GCRSim 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 (BNL), 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, the Brigham & Women's Hospital Department of Radiology, and the NASA Ames Research Center. For Aim 1, we have now completed the irradiation, MRI scanning, behavioral analyses, sacrifice, and tissue collection of all mice. We bred and aged two identical cohorts of 114 mice per cohort, including female and male Alzheimer's-like transgenic (Tg) mice and wildtype (WT) mice, staggered ~5-6 months apart. Mice underwent pre-irradiation (IRR) MRI scans of brain and heart at 3.5 months of age, were transported to Brookhaven National Laboratory (BNL) for low-dose GCRsim IRR (0.5 or 0.75 Gy; WT and Tg) or gamma IRR (0.75 or 2 Gy; WT only), and were returned to BWH where they later underwent behavioral testing and post-IRR MRI scans prior to sacrifice and tissue harvest at 13 months of age. Of the 228 mice at the start of the study, a total of 184 mice survived until the end of the study. Roughly half of the female Tg died prematurely, regardless of radiation exposure, similar to what we and others have previously observed. Male Tg and all WT mice had few, if any, premature deaths. A total of 124 of the mice underwent extensive

Task Progress:	behavioral testing at 12-13 months of age, while 60 mice underwent follow-up MRI scanning of the brain and heart. In terms of behavior, GCRsim and gamma IRR worsened spatial memory in male WT mice but not females or Tg mice. This is similar to our previous findings with single ion IRR (56-iron or protons) which also worsened memory in male mice but not females and suggests that low doses of space-like radiation induced sex-specific, long-lasting effects on brain function. Male WT mice had reduced sensorimotor gating compared to female WT mice without radiation, while both GCRsim and gamma IRR reduced sensorimotor gating in female WT mice. In the rotarod test for motor coordination, female Tg mice were able to hold onto the rotating rod longer than all other mice but GCRsim IRR caused them to fall off the rod sooner. Male Tg mice exposed to low-dose GCRsim stayed on the rod longer, suggesting they had improved motor coordination. Gamma IRR had no effect on motor coordination in male or female WT mice. Male Tg mice exposed to GCRsim were better able to resist fatigue (i.e., had better endurance) in the wire hanging test than non-irradiated mice. Importantly, no radiation-specific effects were observed for fear learning and memory, startle response, or anxiety- or depressive-like behaviors in any of the mouse groups. Comparison of pre- to post-IRR brain MRI scans indicated reduced cortical volume in female and male WT mice exposed to GCRsim and gamma IRR and increased ventricular volume in female WT and male Tg mice exposed to GCRsim, both of which are suggestive of brain atrophy. In contrast, GCRsim IRR increased hippocampal volume in male WT and male Tg mice while gamma IRR increased it in female and male WT mice. We will stain brain sections to confirm hippocampal volume changes and look for signs of neurogenesis or peripheral cell infiltration. Amyloid-beta, a protein that aggregates and forms plaques in Alzheimer's disease brain, was higher in female Tg than male Tg mouse brain, as seen previously with this mouse model, but GCRsim IRR had no effect. Previously, we found that Abeta levels were increased in male Tg mice exposed to iron IRR, a small component of the GCRsim exposure. Further brain analyses are underway. Regarding the cardiac studies, the MRI scans revealed no radiation-specific effects on heart structure or function. Our collaborators at THI measured gene expression changes in the heart and kidney. Interestingly, there were strong, long-lasting, radiation-induced gene expression changes in the heart and kidney following low-dose GCRsim exposure, but less so with gamma IRR. In particular, GCRsim IRR reduced the expression of genes in the heart needed to break down fats to use as energy and to transport glucose in WT and Tg mice. It also reduced genes involved in pathological tissue remodeling and fibrosis and inflammatory pathways. In kidney, GCRsim IRR reduced the expression of genes involved in DNA damage repair and pathological tissue remodeling and fibrosis, and increased expression of a glycoprotein found on immune cells to facilitate their transmigration across endothelial cells. Mouse hearts and kidneys are being examined histologically. For Aim 2, we were somewhat delayed by the COVID-19 pandemic. We have now bred and aged 272 novel Alzheimer's-like amyloid knock-in (KI) mice that express either human APOE E3 or E4, the latter of which is the strongest risk factor for Alzheimer's disease after aging. Equal numbers of female and male mice were subjected to low-dose GCRsim IRR at BNL in May 2021. A second cohort will be subjected to GCRsim and gamma IRR at BNL in June 2021. Pre-IRR MRI scans were performed on a subset of 32 mice. Behavioral testing, MRI follow-up scans, and analysis of blood, brain, heart and kidney will begin in Spring 2022. For Aim 3, we have completed several studies at BNL using human 3D neural cultures derived from immortalized progenitor cells, called ReNcells, some of which express Alzheimer's disease-associated mutations. This "brain-in-a-dish" paradigm was developed by our collaborators, Drs. Rudy Tanzi and Doo Yong Kim at MGH. We demonstrated the feasibility of transporting these cultures between Boston and Long Island and have collected data on how radiation affects disease progression. In general, we see a consistent increase in amyloid-beta protein levels following gamma IRR but not GCRsim IRR. Amyloid production was not elevated, suggesting that gamma IRR caused an impairment in breakdown or clearance of amyloid protein. Thus far, we have seen very little change in tau or phosphorylated tau protein (which is one of the hallmarks of Alzheimer's disease). Radiation increased the release of inflammatory molecules called cytokines. Adding brain immune cells called microglia to the cultures after GCRsim IRR resulted in migration of the microglia towards the neurons in wildtype, non-Alzheimer's cell cultures and increased secretion of immune molecules after gamma IRR in Alzheimer's-like cell cultures. Cytokines were elevated after adding microglia, regardless of whether the neural cultures had been exposed to radiation or not. In addition, we recently irradiated human stem cell (iPSC)-derived brain cells with different forms of Apolipoprotein E including APOE4, APOE3, APOE2, and cells lacking APOE. Gamma radiation exposure increased the overall levels of insoluble amyloid-beta but reduced the insoluble (aggregated) amyloid-beta 42/40 ratio in the fluid bathing the E4, E2, and KO cell cultures. In contrast, gamma radiation increased the soluble amyloid-beta 42/49 ratio in all 4 cell lines while GCRsim increased it in the E3 and E2 lines. A subset of these cells was shipped to the NASA Ames Research Center for single cell RNA sequencing by our collaborators. Lastly, our THI collaborators shipped human stem cell (iPSC)-derived cardiomyocytes and endothelial cells to BNL where we exposed them to GCRsim and gamma radiation in May 2021. A duplicate experiment will be run in June 2021. The cells were shipped back to THI in Houston to look for radiation-induced changes in gene expression, cell morphology and for cardiomyocytes, electrical changes. 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.
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