Fiscal Year:	FY 2017	**Task Last Updated:**	FY 11/28/2016
PI Name:	O'Banion, Kerry M.D., Ph.D.		
Project Title:	Impact of Space-Radiation Induced Alterations on Toxic Protein Accumulation Associated with Neurodegenerative Disease		
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) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	Rochester	**State:**	NY
Zip Code:	14642-0001	**Congressional District:**	25
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
Start Date:	01/29/2016	**End Date:**	01/28/2020
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	November 2016: There have been no changes to key personnel.		
COI Name (Institution):	Deane, Rashid Ph.D. (University of Rochester) Majewska, Anna Ph.D. (University of Rochester) Williams, Jacqueline Ph.D. (University of Rochester)		
Grant/Contract No.:	NNX16AE07G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	In addition to the risk of cancer, there is concern that prolonged exposure of astronauts to deep space radiation will lead to degenerative changes in different organ systems, including the brain. Indeed we previously demonstrated that space radiation impaired cognitive performance and exacerbated Alzheimer's disease (AD) pathology in a widely used mouse model of AD. Accumulation of the toxic peptide amyloid-ß occurs in AD and has been clearly established as an inherited cause of the disease. Space radiation at relatively modest doses elicits chronic inflammation and oxidative stress responses that alter normal brain function and may contribute to amyloid-ß accumulation by inhibiting normal clearance mechanisms. Recent data from our laboratory shows reduced clearance of amyloid-ß in mouse brain many months after exposure to space radiation. Thus, we hypothesize that radiation exacerbates Alzheimer's disease pathology by altering the ability of the brain to remove amyloid-ß. To address this hypothesis we propose experiments that explore three possible cellular mechanisms linking radiation-induced neuroinflammation to reduced amyloid-ß clearance. We also propose to determine whether a drug that reduces brain inflammation and enhances amyloid-ß clearance can mitigate radiation-induced changes in Alzheimer's pathology and cognitive decline in a mouse model of the disease. Taken together, these studies will lead to a better understanding of the biological mechanisms underlying risks for neurodegenerative disease after space radiation exposure.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research explores mechanisms by which toxic proteins involved in neurodegenerative diseases might accumulate in brain tissue following radiation exposure. Our results in mice using space-relevant radiation types and doses may inform about possible risks to individuals exposed to radiation on Earth whether during medical procedures or unplanned accidental exposures.
Task Progress:	In this first year of the grant we have carried out irradiations at NASA Space Radiation Laboratory (NSRL) for 3 of our proposed experiments. More specifically, during NSRL Run 16B, we irradiated 108, 6-month old C57BL/6 male mice with 50 cGy 600 MeV/µ iron particles on June 1, 2016 for Experiment 1.1, and irradiated another 120, 6-month old C57BL/6 male mice with different doses of silicon (10 and 50 cGy, 300 MeV/µ; May 31, 2016), iron (10 and 50 cGy, 600 MeV/µ; June 1, 2016), or 100 cGy of a modeled SPE (solar particle event) spectra of protons (June 2, 2016) for Experiment 3.1. Our team returned to Brookhaven on October 11, 2016, during NSRL Run 16C to expose 126 mice to 50 cGy of 600 MeV/µ iron particles for use in Experiment 2.1. In all cases appropriate numbers of sham-irradiated mice were similarly processed at the NSRL (e.g., placed in holders for similar times), but not exposed to radiation. All mice were shipped back to Rochester for further experiments. During these experiments, some mice were lost due to aggressive behavior within specific cages. We worked with Veterinary staff at both Brookhaven and Rochester to try and reduce the prevalence of this problem. Reducing the number of times that cages are changed at Brookhaven appeared to help reduce male aggression during NSRL 16C. We completed our first analysis of Aß clearance, described in Experiment 1.1, in early October of this year. This represents a 4-month time point following irradiation. Irradiated (50 cGy 600 MeV/µ iron) and sham-irradiated mice were surgically implanted with a cannula into the striatum. Eighteen hours later, mice were injected via the cannula with 125I-labeled Aß1-40 and 14C-labeled inulin and sacrificed at 5 or 30 min post-injection for whole brain counting of retained radioactivity. In sham-irradiated (Control) mice injected 125I-Aß1-40 was rapidly cleared from brain, with 37% remaining after 30 min. In contrast, this clearance was significantly diminished with 61% remaining in brain after 30 min in irradiated mice. From a mechanistic point, injection of antibody to LRP-1 significantly blocked clearance in control, but not irradiated mice, suggesting a defect of receptor-mediated transport of Aß across the blood brain barrier. Clearance of inulin was also affected by radiation: there was a significant decline in 14C-Inulin after 30 min in control mice that was completely absent in irradiated mice. These results replicate previous data with C57BL/6 mice 10 months after irradiation with 50 cGy iron particles. Additional analyses of these same mice will be carried out at 8 and 12 months of age to complete Experiment 1.1. Analyses of mice irradiated 6 months ago with multiple ions to examine microglial function will be carried out in December 2016 (Experiment 3.1) and mice irradiated with iron will be available to start gathering data related to Experiment 2.1 (CSF clearance) in February 2017.
Bibliography Type:	Description: (Last Updated: 02/16/2024)
Abstracts for Journals and Proceedings	O'Banion MK, Belcher E, Duclos L, Hinkle J, Olschowka JA, Williams JP. "Impact of Space Radiation Induced Neuroinflammation on Alzheimer and Parkinson Disease Pathology." Presented at 2016 NASA Human Research Program Investigators' Workshop, and 27th Annual Space Radiation Investigators' Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators' Workshop, and 27th Annual Space Radiation Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016
Abstracts for Journals and Proceedings	O'Banion MK, Deane R, Majewska A, Williams JP, Olschowka JA. "Impact of Space-Radiation Induced Alterations on Toxic Protein Accumulation Associated with Neurodegenerative Disease." Presented at 2016 NASA Human Research Program Investigators' Workshop, and 27th Annual Space Radiation Investigators' Workshop, Galveston, TX, February 8-11, 2016. 2016 NASA Human Research Program Investigators' Workshop, and 27th Annual Space Radiation Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016
Abstracts for Journals and Proceedings	O'Banion MK, Deane R, Majewska A, Williams JP, Olschowka JA. "Impact of Space-Radiation Induced Alterations on Toxic Protein Accumulation Associated with Neurodegenerative Disease." Presented at 2017 NASA Human Research Program Investigators' Workshop, and 28th Annual Space Radiation Investigators' Workshop, Galveston, TX, January 23-26, 2017. 2017 NASA Human Research Program Investigators' Workshop, and 28th Annual Space Radiation Investigators' Workshop, Galveston, TX, January 23-26, 2017. , Jan-2017