Fiscal Year:	FY 2019	**Task Last Updated:**	FY 12/02/2018
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 Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	kerry_obanion@urmc.rochester.edu	**Fax:**	FY 585-756-5334
PI Organization Type:	UNIVERSITY	**Phone:**	585-275-5185
Organization Name:	University of Rochester		
PI Address 1:	Box 603		
PI Address 2:	601 Elmwood Ave		
PI Web Page:			
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:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	3	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**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 third year of the grant we carried out irradiations at NASA Space Radiation Laboratory (NSRL) for 2 of our proposed experiments and a new supplemental experiment. More specifically, during NSRL Run 18A, we irradiated 58, 4-month old APP/PS1 male and female mice with 50 cGy 600 MeV/µ iron particles for Experiment 4.2; during NSRL-18B we irradiated another 48, 4-month old APP/PS1 male and female mice with iron (50 cGy, 600 MeV/µ) for Experiment 4.1. Our team returned to Brookhaven during NSRL18C to expose 57 APP/PS1 and 68 wild-type (C57BL/6) mice to 500 mGy of the NSRL-GCRSim field, given acutely as one dose (October 8) or in 24 fractions (20.83 mGy/day; 6 days a week for 4 weeks; Oct 8-Nov 3). 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. We completed our initial analysis of microglial proliferation in brain sections following needle stab injury and found no clear evidence for changes in this response, six months following particle irradiation with iron (50 cGy, 600 MeV/µ, silicon (50 cGy, 300 MeV/µ), or protons (100 cGy, SPE). Additional analyses of microglial morphology, activation, and gene expression are in process. These studies were all carried out with male mice. Similar studies are planned for female mice to be irradiated in the coming grant period (NSRL-19B) as an additional supplemental study. Studies to examine effects of radiation on microglial phagocytosis of amyloid plaques (Experiment 3.2) are planned in the next grant period with irradiation of APP/PS1 mice taking place during NSRL-19B. We completed our first experiment (4.2) with irradiated APP/PS1 mice that had been treated with Fluvastatin. In these mice, Abeta clearance measured by infusion of 125l-labeled Abeta1-40 was reduced 6 months following 50 cGy iron (600 MeV/µ) exposure, and this effect was mitigated by 2 months of Fluvastatin treatment. These results are consistent with findings reported last year that particle radiation reduces active Abeta transport, which is primarily due to low-density lipoprotein (LDL) receptor-related protein-1 (LRP1) activity. Analyses of LRP1 expression inmicrovessels isolated from irradiated brain as well as other measures of cerebral vasculature are in progress. Mice run in Experiment 4.1 are currently being treated with Fluvastatin and will be analyzed early in the coming grant period for amyloid plaque load and other measures related to overt Alzheimer-associated pathology. We plan to combine results from these two studies with results from Aims 1 and 2 to prepare and submit a manuscript this next grant period.
Bibliography Type:	Description: (Last Updated: 03/09/2021)
Abstracts for Journals and Proceedings	O'Banion MK, Deane R, Belcher E, Hinkle J, Dionisio-Santos D, Williams JP, Olschowka JA. "Impact of space-radiation induced alterations on toxic protein accumulation associated with neurodegenerative disease." Presented at 2018 NASA Human Research Program Investigators' Workshop, and 29th Annual Space Radiation Investigators' Workshop, Galveston, TX, January 22-25, 2018. Proceedings abstracts. 2018 NASA Human Research Program Investigators' Workshop, and 29th Annual Space Radiation Investigators' Workshop, Galveston, TX, January 22-25, 2018. , Jan-2018
Abstracts for Journals and Proceedings	Belcher E, Sweet T, Leffler K, Olschowka J, Williams J, O'Banion MK. "Cranial gamma irradiation impairs injury-induced microglia proliferation." 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. Proceedings abstracts. 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. , Sep-2018