Fiscal Year:	FY 2021	**Task Last Updated:**	FY 02/25/2021
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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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:**	11/28/2020
No. of Post Docs:	0	**No. of PhD Degrees:**	3
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
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 11/28/2020 per NSSC information (Ed., 8/25/20)		
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:	Summary of Major Findings Aim 1 • Abeta clearance was reduced at 4, 8, and 12 months following 50 cGy 600 MeV/µ iron exposure • An anti-LRP1 antibody inhibited Abeta clearance • We were not able to reproducibly demonstrate changes in LRP1 protein expression in isolated microvessels by Western blot; we believe this is a technical issue related to variability in vessel isolation • Abeta clearance was reduced at 4 months following exposure to silicon (50 cGy 300 MeV/µ), protons (100 cGy SPE), and a lower dose of iron (10 cGy) Aim 2 • For nearly all the conditions tested, inulin clearance was not affected by radiation • Glymphatic flow assessed by penetration of radiotracers from the CSF (cerebrospinal fluid) was not influenced by 50 cGy iron (600 MeV/µ), 4 months post-irradiation • We were not able to show clear evidence of changes in astrocyte endfeet association with the vasculature after radiation Aim 3 • Unlike our findings with low-LET (linear energy transfer) radiation (at higher doses), initial analysis of microglial proliferation in irradiated male mice after cortical needle stab injury showed variable results, but suggest that low radiation doses increased proliferation • Our RNAseq analysis of microglia, six months after irradiation showed fewer changes with space radiation (iron, silicon or protons) than a high dose (20 Gy) of low-LET (linear energy transfer) radiation • RNAseq analysis of microglia, 6 months after space irradiation, revealed more changes in male mice than in female mice • Interestingly, with both types of radiation there was a greater number of downregulated transcripts Aim 4 • Fluvastatin treatment mitigates reduced Abeta clearance using radiolabeled tracers in mice irradiated with 50 cGy iron (600 MeV/µ). This is a very exciting finding that is consistent with previously observed effects of statin treatment on LRP1 dependent Abeta transport. • We observed a trend for reduced novel object performance in female APP/PS1 mice irradiated with 50 cGy iron (600 MeV/n), but did not see clear effects of radiation or fluvastatin in irradiated male APP/PS1 mice • Initial analysis of amyloid deposition in this experiment showed no effect of radiation (50 cGy iron, 600 MeV/n) in female APP/PS1 mice and variable effects in male mice, which were run in three separate groups
Bibliography Type:	Description: (Last Updated: 02/16/2024)
Articles in Peer-reviewed Journals	Belcher EK, Sweet TB, Karaahmet B, Dionisio-Santos DA, Owlett LA, Leffler KA, Janelsins MC, Williams JP, Olschowka JA, O'Banion MK. "Cranial irradiation acutely and persistently impairs injury-induced microglial proliferation." Brain Behav Immun – Health. 2020 Apr 4:100057.https://doi.org/10.1016/j.bbih.2020.100057 , Apr-2020
Articles in Peer-reviewed Journals	Owlett L, Belcher E, Dionisio-Santos D, Williams JP, Olschowka JA, O'Banion MK. "Space radiation does not alter amyloid or tau pathology in the 3xTg mouse model of Alzheimer's disease." Life Sci Space Res. 2020 Nov;27:89-98. https://doi.org/10.1016/j.lssr.2020.08.001 , Nov-2020

Articles in Peer-reviewed Journals	Zablotska LB, Zupunski L, Leuraud K, Lopes J, Hinkle J, Pugeda T, Delgado T, Olschowka J, Williams J, O'Banion MK, Boice JD, Jr., Cohen SS, Mumma MT, Dauer LT, Britten RA, Stephenson S. "Radiation and CNS effects: Summary of evidence from a recent symposium of the Radiation Research Society." Int J Radiat Biol. 2022 Nov 11:1-11. https://doi.org/10.1080/09553002.2023.2142984 ; PMID: 36318723 , Nov-2022