

<b>Fiscal Year:</b>	FY 2018	<b>Task Last Updated:</b>	FY 11/24/2017
<b>PI Name:</b>	O'Banion, Kerry M.D., Ph.D.		
<b>Project Title:</b>	Impact of Space-Radiation Induced Alterations on Toxic Protein Accumulation Associated with Neurodegenerative Disease		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>			
<b>Program/Discipline--Element/Subdiscipline:</b>	HUMAN RESEARCH--Radiation health		
<b>Joint Agency Name:</b>		<b>TechPort:</b>	No
<b>Human Research Program Elements:</b>	(1) <b>SR</b> :Space Radiation		
<b>Human Research Program Risks:</b>	(1) <b>Bmed</b> :Risk of Adverse Behavioral Conditions and Psychiatric Disorders		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Zip Code:</b>	14642-0001	<b>Congressional District:</b>	25
<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
<b>Start Date:</b>	01/29/2016	<b>End Date:</b>	01/28/2020
<b>No. of Post Docs:</b>	0	<b>No. of PhD Degrees:</b>	0
<b>No. of PhD Candidates:</b>	3	<b>No. of Master' Degrees:</b>	0
<b>No. of Master's Candidates:</b>		<b>No. of Bachelor's Degrees:</b>	0
<b>No. of Bachelor's Candidates:</b>		<b>Monitoring Center:</b>	NASA JSC
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<b>Flight Program:</b>			
<b>Flight Assignment:</b>			
<b>Key Personnel Changes/Previous PI:</b>	November 2016: There have been no changes to key personnel.		
<b>COI Name (Institution):</b>	Deane, Rashid Ph.D. ( University of Rochester ) Majewska, Anna Ph.D. ( University of Rochester ) Williams, Jacqueline Ph.D. ( University of Rochester )		
<b>Grant/Contract No.:</b>	NNX16AE07G		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

<b>Task Description:</b>	<p>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-<math>\beta</math> 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-<math>\beta</math> accumulation by inhibiting normal clearance mechanisms. Recent data from our laboratory shows reduced clearance of amyloid-<math>\beta</math> 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-<math>\beta</math>. To address this hypothesis we propose experiments that explore three possible cellular mechanisms linking radiation-induced neuroinflammation to reduced amyloid-<math>\beta</math> clearance. We also propose to determine whether a drug that reduces brain inflammation and enhances amyloid-<math>\beta</math> 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.</p>
<b>Rationale for HRP Directed Research:</b>	
<b>Research Impact/Earth Benefits:</b>	<p>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.</p>
<b>Task Progress:</b>	<p>In this second year of the grant we carried out three new irradiation campaigns. As part of NASA Space Radiation Laboratory (NSRL) NSRL-17A, we irradiated 180, 6-month old C57BL/6 male mice with different doses of silicon (10 and 50 cGy, 300 MeV/<math>\mu</math>), iron (10 and 50 cGy, 600 MeV/<math>\mu</math>), or 100 cGy of a modeled SPE (solar particle event) spectra of protons for Experiment 1.2. Another 108 mice served as sham controls. On April 18, 2017, we irradiated groups of 20 6-month old C57BL/6 female mice with 10 and 50 cGy Fe (600 MeV/<math>\mu</math>) plus twenty sham controls, as an add-on experiment to assess effects on A<math>\beta</math> clearance in females. This experiment was not part of our original proposal, but was felt to be important given our early positive findings in male mice. Because of challenges associated with our cannulation procedures, we irradiated a further set of female mice during NSRL-17C (October 24, 2017). 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. Analyses completed during this grant period included A<math>\beta</math> clearance for mice 8 and 12 months following iron irradiation (Experiment 1.1), A<math>\beta</math> clearance for mice 4 months post-irradiation with multiple ions and doses (Experiment 1.2, see above), and A<math>\beta</math> influx, a measure of interstitial fluid convective flow, in mice 4 and 8 months following exposure to 50 cGy 600 MeV/<math>\mu</math> iron particles (Experiment 2.1). For studies of A<math>\beta</math> clearance, irradiated 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 A<math>\beta</math>1-40 and 14C-labeled inulin and sacrificed 30 min post-injection for whole brain counting of retained radioactivity. At all time points examined (4, 8, and 12 months post-irradiation with 50 cGy iron) we found clear evidence of diminished A<math>\beta</math> clearance with radiation. This also occurred in mice irradiated with silicon or protons mimicking an SPE. 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 A<math>\beta</math> across the blood brain barrier. Current studies are focused on measuring LRP-1 protein and mRNA levels in microvessels isolated from sham and irradiated mice. In contrast, we found less evidence of radiation-induced changes in convective flow: clearance of inulin from the brain was not consistently altered by radiation; moreover, direct analysis of radiolabeled A<math>\beta</math> and inulin influx into the brain showed no changes with radiation. We also have not detected clear radiation-induced changes in astrocyte endfoot protein expression critical for regulating convective flow. Thus this passive mechanism for A<math>\beta</math> clearance from the brain appears to be less affected by radiation than active clearance through the blood brain barrier.</p> <p>Analyses related to microglial function (Aim 3) are still in process. In the coming year we will be carrying out studies using APP/PS1 transgenic mice (Aims 3 and 4).</p>
<b>Bibliography Type:</b>	Description: (Last Updated: 03/09/2021)