Fiscal Year:	FY 2014	**Task Last Updated:**	FY 03/19/2015
PI Name:	Goldstein, Lee M.D., Ph.D.		
Project Title:	Effects of Space Radiation on Hippocampal-Dependent Learning and Neuropathology in Wild-Type and Alzheimer's Disease Transgenic Mice		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
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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Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2011 Space Radiobiology NNJ11ZSA001N
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No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 2/28/2017 (previously 8/31/2016) per S. Monk/LaRC (Ed., 9/20/16) NOTE: End date changed to 8/31/2016 per S. Monk/HRP and NSSC information (Ed., 6/21/16) NOTE: End date changed to 3/31/2016 per NSSC information (Ed., 7/9/15) NOTE: Extended to 1/21/2016 per PI and NSSC information (Ed., 3/12/2015)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Blakely, Eleanor (Lawrence Berkeley National Laboratory) Moncaster, Juliet (Boston University) Stanton, Patric (New York Medical College)		
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Task Description:	The hippocampus and dentate gyrus are critically important brain regions required for long-term memory formation. Damage to these critical brain regions contributes to memory deficits in patients with Alzheimer's disease. The hippocampus and dentate gyrus are also notable as sites where brain stem cells differentiate into new neurons throughout life, a process called neurogenesis. Exposure to space radiation can result in impairments in learning and long-term reduction in hippocampal neurogenesis. It is unknown how radiation causes these impairments and whether and by what mechanism(s) radiation exposure might predispose individuals to develop Alzheimer's disease. This proposal will utilize a well-characterized and widely used Alzheimer's disease transgenic mouse model (Tg2576) to address the following research objectives: (1) examine the long-term impact of space radiation (SR) on hippocampal-dependent spatial learning and memory, (2) evaluate the potential of SR to accelerate Alzheimer's disease pathogenesis and neuropathology, (3) evaluate a novel non-invasive laser-based eye scanner to detect and monitor molecular changes in the lens of the eye induced by radiation exposure and Alzheimer's disease pathology (Goldstein, et al., Lancet, 2003). A complementary companion study will utilize the same cohort of animal subjects to: (1) evaluate electrical communication between neurons, and changes in function and fine structure of neurons, including dendritic spines where synaptic contacts enable neuronal communication, (2) determine whether SR, in reducing neurogenesis, also alters the functionality of newly-born neurons, and (3) assess whether SR differentially affects electrical or physical function of neurons, and/or accelerates the Alzheimer's disease process. Our proposed studies directly address key objectives of the NASA Human Space Flight Program, including determination of potential space-related SR dependencies related to late central nervous system (CNS) risks such as early-onset dementia or Alzheimer's disease, assessment of SR effects on molecular, cellular, and tissue environment changes in hippocampus indicative of increased risk of dementia or Alzheimer's disease, and evaluation of biological models of Alzheimer's disease or other forms of dementia that occur in humans. The existing knowledge gap is immense and presents a major obstacle to rational assessment of short- and long-term risk to the central nervous system posed by SR exposure expected during extended human space travel. Our experiments will examine, for the first time, the mechanisms by which SR impairs synaptic function in normal brain, assess whether SR does, in fact, enhance long-term risk of Alzheimer's disease, and provide an experimental system to identify and evaluate new radiation countermeasures. The proposed interdisciplinary research program will provide an integrated scientific foundation to assess and reduce SR-induced risk to the brain, thus enabling a safe path forward for extended human space exploration.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This project investigates Alzheimer's Disease (AD) vulnerability in the setting of exposure to low-dose particle space radiation. The goal of extended human space flight is predicated on establishing a solid scientific foundation for rational assessment of Central Nervous System (CNS) risk from exposure to space radiation. The same argument applies to development of prophylactic countermeasures. Exposure to particle radiations during long-duration space travel may induce subtle but deleterious late effects in neuronal function and propensity for neurodegenerative diseases, including AD. While acute CNS damage is a hallmark injury following exposure to high-dose radiation, investigation of late effects following exposure to low-dose particle space radiation may predispose the brain to development of slowly progressive age-dependent neurodegenerative disease. Moreover, if an AD diathesis is induced by space radiation exposure, the need for effective countermeasures will be of paramount importance for the human space flight program. In this project, we are using the well-characterized Tg2576 AD transgenic mouse model (Hsiao et al., 1996) to determine whether and to what extent exposure to low doses of 28Si and 56Fe particle radiation influence AD risk, latency, progression, and penetrance.
Task Progress:	Our research team is continuing to investigate the effects of space radiation on synaptic plasticity and cognition in C57BL/J6 mice and Tg2576 transgenic mouse model of Alzheimer’s Disease. We are focusing on evaluation of both acute and long- effects of space radiation on spatial learning and memory retrieval. Results of these ongoing studies also allow us to perform clinicopathological correlation of neurophysiological and cognitive changes with neuropathological endpoints in relevant brain regions. We have previously reported related long-term changes in the brain following exposure to other forms of low-intensity neurotrauma (Goldstein LE, et al., Science Transl Med, 2012). Our NASA-funded study results indicate that C57B6/J6 mice, 4 months-of-age, irradiated with single-bolus 56Fe (600 MeV/u; 181 keV/µm; 100 cGy vs 0 cGy sham control) indicate very long-term (>20 months post-irradiation) neurocognitive changes following single low-dose space radiation exposure. Space radiation effects on hippocampal-dependent spatial learning and memory appear to be functionally specific as locomotion, exploratory behavior, and anxiety (elevated plus maze and thigmotaxis) were unaffected in the same mice. Next, we evaluated the long-term effects of 56Fe GCR (galactic cosmic ray) irradiation on long-term potentiation (LTP) of synaptic transmission in hippocampal Schaffer collateral CA1 synapses. In keeping with the long-term cognitive effects of GCR exposure noted above, we observed significant long-term (>20 mos) alterations in theta burst-stimulated and chemically evoked cAMP-dependent LTP at Schaffer collateral synapses in the hippocampal CA1 field. Taken together, these effects are consistent with long-term GCR-induced alterations in synaptically activated and synaptic-independent LTP that likely underpin the observed space radiation-related changes in hippocampal-dependent spatial learning and memory retrieval. Our observation has important implications for acute and chronic effects of space radiation exposure on brain function during long-duration human space travel beyond the Earth’s magnetosphere. Our next Brookhaven National Laboratory (BNL) campaign allowed us to investigate possible sources of acute injury that might trigger chronic changes in neurophysiological and cognitive function. We exposed C57BL/J6 mice, 4 months-of-age, to 28Si (300 MeV/u, 70 keV/µm, 100 cGy, or 0 cGy sham control). Mice were sacrificed and brain inflammatory responses analyzed by flow cytometry (+3 days post-irradiation). We found that while space radiation does not alter microglia morphology or increase monocyte infiltration into the brain, we did detect a significant increase in CNS-infiltrating F4/80+ macrophage. Results of these studies will be included in a paper that we are preparing now with collaborator Patric Stanton, Ph.D., New York Medical College (NASA NNX13AB66G).

Bibliography Type:	Description: (Last Updated: 03/10/2021)