Fiscal Year:	FY 2017	**Task Last Updated:**	FY 01/29/2018
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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Zip Code:	02118	**Congressional District:**	8
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2011 Space Radiobiology NNJ11ZSA001N
Start Date:	09/01/2011	**End Date:**	02/28/2017
No. of Post Docs:	3	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
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 Ph.D. (Lawrence Berkeley National Laboratory) Moncaster, Juliet Ph.D. (Boston University) Stanton, Patric Ph.D. (New York Medical College)		
Grant/Contract No.:	NNX11AR05G		
Performance Goal No.:			
Performance Goal Text:			

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. Reference Goldstein LE, Muffat JA, Cherny RA, Moir RD, Ericsson MH, Huang X, Mavros C, Coccia JA, Faget KY, Fitch KA, Masters CL, Tanzi RE, Chylack LT Jr, Bush AI. Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. Lancet. 2003 Apr 12;361(9365):1258-65.
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. Reference Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science. 1996 Oct 4;274(5284):99-102.
Task Progress:	[Ed. note: compiled from PI's final progress report submitted June 2017] This project investigated brain vulnerability in the setting of exposure to low-dose GCR (galactic cosmic radiation). Extended human space flight is predicated on establishing a solid scientific foundation for rational assessment of CNS risk and development of prophylactic countermeasures relevant to GCR exposure expected during long-duration human space travel. This information represents a critical prerequisite for mission success of long-duration human space travel beyond the Earth’s magnetosphere. While acute CNS damage is a hallmark of exposure to high-dose ionizing radiation, the effects of low-dose GCR on brain structure and function remain largely unknown. An emerging body of evidence suggests that low-dose GCR induces deleterious effects on neuronal function and accelerates brain pathologies associated with AD and other neurodegenerative diseases. Our research involving neuropathological analysis of post-mortem human brains and experimental animals indicates that exposure to low-intensity neurotrauma triggers specific neurodegenerative disease mechanisms and pathologies that degrade brain structure and function (Goldstein et al., Science Transl Med, 2012; McKee et al., Brain, 2013 ; Kondo et al., Nature, 2015). These effects manifest acutely, progress chronically, and trigger brain pathologies, cognitive dysfunction, and frank neurodegeneration. Experimental evidence developed during the course of this NASA-funded project indicate that the same pathogenic pathways and mechanisms are activated in laboratory mice exposed to low-dose GCR. We used non-transgenic C57BL/6 mice and Tg2576 AD transgenic mice to determine whether and to what extent exposure to low-dose GCR influences brain structure, function, pathology, risk, latency, progression, and penetrance relevant to these questions. The project generated new information that is directly relevant to maintaining astronaut health and optimal performance during and after long-duration space travel. Project insights are critically important for successful long-duration human space travel and the NASA Human Space Program.

	Further studies are warranted to confirm and extend project results and translational strategies. Goldstein LE, Fisher AM, Tagge CA, Zhang XL, Velisek L, Sullivan JA, Upreti C, Kracht JM, Ericsson M, Wojnarowicz MW, Goletiani CJ, Maglakelidze GM, Casey N, Moncaster JA, Minaeva O, Moir RD, Nowinski CJ, Stern RA, Cantu RC, Geiling J, Blusztajn JK, Wolozin BL, Ikezu T, Stein TD, Budson AE, Kowall NW, Chargin D, Sharon A, Saman S, Hall GF, Moss WC, Cleveland RO, Tanzi RE, Stanton PK, McKee AC. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med. 2012 May 16;4(134):134ra60. [non-NASA supported] McKee AC, Carreras I, Hossain L, Ryu H, Klein WL et al. (2008) Ibuprofen reduces Abeta, hyperphosphorylated tau and memory deficits in Alzheimer mice. Brain Res 1207: 225-236. [non-NASA supported] Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature. 2015 Jul 23;523(7561):431-436. [non-NASA supported]
Bibliography Type:	Description: (Last Updated: 03/10/2021)
Articles in Peer-reviewed Journals	Miry O, Zhang XL, Vose LR, Gopaul KR, Subah G, Moncaster JA, Wojnarowicz MW, Fisher AM, Tagge CA, Goldstein LE, Stanton PK. "Life-long brain compensatory responses to galactic cosmic radiation exposure." Sci Rep. 2021 Feb 22;11(1):4292. https://doi.org/10.1038/s41598-021-83447-y ; PMID: 33619310; PMCID: PMC7900210 , Feb-2021