Fiscal Year:	FY 2013	**Task Last Updated:**	FY 08/16/2013
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:			
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No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
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Flight Program:			
Flight Assignment:	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 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.
	A. Project Hypotheses & Specific Aims Project Hypotheses We hypothesize that exposure to low-dose particle space radiation will negatively and synergistically impact: (i) hippocampal-dependent learning and memory, and (ii) Alzheimer’s disease (AD)-linked pathology in the brain and lens. We anticipate that these effects will be dose- and time-dependent. Furthermore, we hypothesize that cerebral microvasculature disruption and reactive neuroinflammation are critical radiation-induced pathogenic mechanisms by which hippocampal neurocognitive dysfunction and age-dependent AD pathology are synergistically accelerated. Understanding of these relationships is essential for rational assessment of CNS risk and efficient development of prophylactic countermeasures for extended human space travel. Specific Aim 1. Identify and characterize the effects of low-dose particle space radiation exposure on hippocampal-dependent spatial learning and memory using the Morris water navigation task (or alternative hippocampal-dependent spatial reference paradigm) in Tg2576 AD transgenic mice compared to age-matched wild-type controls. Specific Aim 2. Identify and characterize the effects of low-dose particle space radiation exposure on AD biochemistry and histopathology in Tg2576 AD transgenic mice compared to age-matched wild-type littermate controls. Specific Aim 3. Identify, characterize, and track the effect of low-dose particle space radiation on AD progression using a novel noninvasive laser-based eye scanner to quantitatively assess AD-linked Aß pathology in the lens. Our team discovered AD-linked Aß pathology in the lenses of human subjects with AD (Goldstein, 2003). We subsequently confirmed identical AD-linked lens pathology and age-dependent Abeta accumulation in Down syndrome (100% risk of developing early-onset AD; (Moncaster, 2010) and Tg2576 mice (Moncaster, submitted). These discoveries led us to develop an innovative scanning laser ophthalmoscope with quasi-elastic light scattering analytical capabilities. This noninvasive instrument allows safe, simple, and extremely sensitive analytical assessment of AD-linked Aß pathology in the lenses of non-anesthetized mice. In a recently completed series of experiments utilizing this noninvasive technology in Tg2576 mice (Moncaster, submitted), we detected and tracked pre-cataractous AD-linked Aß lens pathology in Tg2576 mice before onset of detectable amyloid pathology in the brain or lens. Our proposal affords a unique opportunity to evaluate this innovative technology in the context of two possibly interactive variables (i.e., low-dose space particle radiation and AD) both of which are primary targets of the proposed research program. Potential for informative covariate and correlative analyses involving other study endpoints (i.e., behavior, histopathology, biochemistry, neurophysiology) is high. This aim is easily justified given the noninvasive nature of the

Task Progress:	technology and the low-risk/high-yield potential of experimental deployment. B. YR2 PROGRESS TO DATE (Sep 1, 2012 through Aug 31, 2013) Fall 2012 Campaign: We whole-body irradiated 3-month-old male and female mice Tg2576 and wild-type controls using Beamline 56Fe (600 MeV/u, 181 keV/µm) at Brookhaven National Laboratory (BNL). These studies were conducted in consultation with NASA and Eleanor Blakely, Ph.D., Senior Staff Biophysicist, Lawrence Berkeley National Laboratory, who serves as Radiobiology Collaborator on this project. We did 0 and 100 cGy. Each group comprised of n=8 mice and will be sacrificed at 18 months-of-age (+14 months s/p irradiation). Behavior in these mice will be assessed at the midpoint between irradiation, and again just prior to sacrifice and tissue harvest. Animal numbers are calculated as follows: 2 groups (Wt, Tg) x 2 genders (F, M) x 1 irradiation types (Fe) x 2 doses (0, 100 cGY) x 1 timepoints (18mos) = 8 groups x 10 per group = 80 mice total. Summer 2013 Campaign: We whole-body irradiated 3-month-old male and female C57Bl/6 mice with Beamline 28Si (300 MeV/u, 70 keV/µm) at BNL using doses 0,10, 50, 100 cGY. Animal numbers were calculated as follows: 2 genders (F, M) x 1 irradiation types (Si) x 4 doses (0,10, 50, 100 cGY) x 2 timepoints (10mos, 18mos) = 16 groups x 10 per group = 160 mice total. Expt objectives: (i) evaluate background effects of 28Si exposure on cerebral microvasculature and neuroinflammation assessed by ultrastructural (EM) neuropathological analysis. Dr. Patric Stanton and a lab member of his assisted and observed this Beamline run. This was the first time at NASA BNL, NSRL and the Goldstein group mentored them through the process. Dr. Stanton has a collaborative NASA grant from which some of the Goldstein mice irradiated at BNL will be shared with Dr. Stanton who will be studying electrophysiological changes in the brain. All mice will be behaviorally assessed on a hippocampal-dependent spatial learning and memory task using the Barnes Maze and evaluated using a battery of neurobehavioral, neuropathological, and biomarker endpoints at selected post-irradiation intervals endpoints as a function of: (i) particle radiation exposure (Z, energy, dose), (ii) genotype (Tg, Wt), (iii) post-exposure interval, (iv) age and gender. Details of each of these assessments are included in the original proposal. See our publication for additional details regarding immunohistochemical, ultrastructural, and neurobehavioral index metrics (Goldstein, 2012, Science Transl Med). YR3 EXPERIMENTAL PLAN Summer 2014 Campaign: We whole-body irradiate 3-month-old male and female mice Tg2576 and wild-type controls using Beamline 28Si (300 MeV/u, 70 keV/µm) at BNL using doses 0, 10, 50, 100 cGY. Each group comprises of n=10 mice and will be sacrificed at 18 months-of-age (+14 months post- irradiation). Behavior in these mice will be assessed at the midpoint between irradiation, and again just prior to sacrifice and tissue harvest. Animal numbers are calculated as follows: 2 groups (Wt, Tg) x 2 genders (F, M) x 1 irradiation types (Si) x 4 doses (0, 10, 50, 100 cGY) x 1 timepoints (18mos) = 16 groups x 10 per group = 160 mice total. Data analysis: All tissue analyses from mice tissues collected in Yr 1-3 will be analyzed using a battery of neuropathological and biomarker endpoints as a function of: (i) particle radiation exposure (Z, energy, dose), (ii) genotype (Tg, Wt), (iii) post-exposure interval, (iv) age and gender. Details of each of these assessments are included in the original proposal. See our publication for additional details regarding immunohistochemical, ultrastructural, and neurobehavioral index metrics (Goldstein, 2012, Science Transl Med). All Barnes Maze neurobehavioral data collected in Yr 1-3 will be analyzed and prepared for publication.
Bibliography Type:	Description: (Last Updated: 03/10/2021)
Abstracts for Journals and Proceedings	Moncaster JA, Wojnarowicz M, Sarangi S, Fisher A, Minaeva O, Cantuti-Castelvetri I, Bjornstad KA, Stanton P, Chang P, Blakely EA, Goldstein LE. "Effects of Space Radiation on Hippocampal-Dependent Learning and Neuropathology in Wild-Type and Alzheimer's Disease Transgenic Mice." Alzheimer's Association International Conference 2013 (AAIC), Boston, MA, July 14-18, 2013. Alzheimer's and Dementia; 2013 Jul;9(4 Suppl):P190. http://dx.doi.org/10.1016/j.jalz.2013.05.330 , Jul-2013