Fiscal Year:	FY 2016	**Task Last Updated:**	FY 04/26/2016
PI Name:	Limoli, Charles Ph.D.		
Project Title:	Charged Particle Effects on Neuronal Injury, Plasticity and Neurodegeneration		
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:	92697-2695	**Congressional District:**	45
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2012 Space Radiobiology NNJ12ZSA001N
Start Date:	01/01/2013	**End Date:**	12/30/2016
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	3
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/30/2016 per S. Monk/LaRC (Ed., 12/11/15)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Hughes, Christopher (University of California, Irvine)		
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Performance Goal No.:			
Performance Goal Text:			
	The space radiation environment poses unique hazards to astronauts since a range of potential complications can result from exposure of the central nervous system (CNS) to these dangerous radiation fields. Damage caused by the traversal of charged particles in space through the brain is likely to elicit alterations to the structure and function of neurons and perturb the critical interactions between multiple cell types in the CNS. Irradiation also elicits a persistent increase in free radicals or “oxidative stress” that will complicate further the recovery of the CNS after exposure. Thus, we believe that exposure to the charged particles in space will cause acute and chronic alterations to the cell types in the brain that are critical for learning and memory, thereby having an adverse effect on the functionality of the CNS. To address the foregoing problems we will measure the impact of charged particle irradiation on neuronal anatomy and function using cultures of human neurons grown in the presence and absence of additional cell types known to be		

Task Description:	critical for proper neuronal function. Studies will also be performed in the presence of antioxidants that can minimize damage from reactive species, providing a useful strategy for gauging the importance of radiation-induced oxidative stress. These cell-based studies will be complemented by animal studies in which similar endpoints will be measured in brain tissue isolated from irradiated mice. One animal model genetically modified to express a neuronal fluorescent marker will be used to measure the subtle structural changes to neurons after irradiation. Another animal model genetically modified to exhibit early onset dementia will be used to gauge how exposure to charged particles found in space might impact the onset and/or severity of neurodegenerative phenotypes. Collectively, these studies will provide new data regarding the consequences of charged particle irradiation in the CNS, data that will be useful in estimating the uncertainties and risks associated with space travel.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	In general, work will characterize adverse effects of ionizing radiation on the CNS and help define potential causes and consequences of radiation-induced dementia.
Task Progress:	Experimental highlights: 1. The Tg(Thy1-EGFP)MJrs/J transgenic mouse strain expresses eGFP in specific subsets of neurons, thereby providing brightly fluorescent neurons for morphometric analyses. Cohorts of 6-month old animals have now been irradiated with 16O and 48Ti ions (600 MeV) at doses of 0, 5, and 30 cGy (NASA Space Radiation Laboratory NSRL 12-13A-C). Animals have been analyzed for behavioral deficits at 6, 12, and 24 weeks after exposure. Data sets for 6 weeks are published and data for the 12 week data are provided in this report. Data derived from animals irradiated 6 months prior are still under analysis, which is nearly complete. Data has confirmed the presence of significant behavioral deficits for each ion at weeks 6 and 12 using the Novel Object Recognition (NOR) and Object in Place (OiP) tasks. 2. All animals described above (i.e., eGFP expressing transgenic mice subjected to 16O and 48Ti ion irradiation) are being processed for the micromorphometric analysis of neurons (see data below). To initiate these labor-intensive studies we have selected to analyze neurons within the medial prefrontal cortex (mPFC) and hippocampal Ca1 and dentate gyrus. These neurons are involved in mediating neurotransmission between cortical and hippocampal circuits and impact performance on the selected behavioral tasks above. New data presented in this progress report illustrates some of the structural changes found after 6 weeks after titanium ion exposure in the CA1 region of the hippocampus. 3. Concurrent with the foregoing analyses, the levels of specific synaptic proteins have now been quantified. Levels of presynaptic synaptophysin are significantly depressed at all times analyzed while the opposite holds true for the level of postsynaptic density-95 (PSD95) protein. These alterations underscore the persistent deficits in the synaptic machinery that occur at relatively low particle fluences, changes that likely elevate the risk of developing impaired cognition that could compromise mission critical activities. 4. Structural and synaptic parameters collected from HZE (high energy) ion irradiated animals have now been used to provide quantitative readouts of developing behavioral decrements. Discrimination indices routinely decrease with reduced spine density and elevated PSD95 puncta, and validate the utility of our experimental approach for quantifying parameters relevant to the estimation of risk for developing various forms of dementia. 5. Genetic strategies designed to ameliorate oxidative stress have been found to minimize the adverse effects of proton irradiation in the brain. Mice that overexpress human catalase targeted to the mitochondria (MCAT) were found to show significantly improved cognition following proton irradiation (0.5, 2 Gy) compared to wild type (WT) mice. Improved cognition was coincident with a preservation of host neuronal morphology, suggesting a mechanism for the neuroprotective phenotype in MCAT mice. 6. We have also undertaken some follow up studies demonstrating the beneficial effects of MCAT expression in the subiculum region of the hippocampus. One month following irradiation of WT and MCAT mice, a range of morphometric parameters were quantified along Golgi-Cox impregnated neurons. Compared to WT mice, subiculum neurons from MCAT mice exhibited increased trends (albeit not statistically significant) toward increased dendritic complexity in both control and irradiated cohorts. However, Sholl analysis of MCAT mice revealed significantly increased arborization of the distal dendritic tree, indicating a protective effect on secondary and tertiary branching. Interestingly, radiation-induced increases in postsynaptic density protein (PSD-95) puncta were not as pronounced in MCAT compared to WT mice, and were significantly lower after the 0.5 Gy dose. As past data has linked radiation exposure to reduced dendritic complexity, elevated PSD-95 and impaired cognition, reductions in mitochondrial oxidative stress have proven useful in ameliorating many of these radiation-induced sequelae.
Bibliography Type:	Description: (Last Updated: 12/13/2023)
Articles in Peer-reviewed Journals	Parihar VK, Allen BD, Tran KK, Chmielewski NN, Craver BM, Martirosian V, Morganti JM, Rosi S, Vlkolinsky R, Acharya MM, Nelson GA, Allen AR, Limoli CL. "Targeted overexpression of mitochondrial catalase prevents radiation-induced cognitive dysfunction." Antioxid Redox Signal. 2015 Jan 1;22(1):78-91. Epub 2014 Jun 20. http://dx.doi.org/10.1089/ars.2014.5929 ; PubMed PMID: 24949841; PubMed Central PMCID: PMC4270160 , Jan-2015
Articles in Peer-reviewed Journals	Parihar VK, Pasha J, Tran KK, Craver BM, Acharya MM, Limoli CL. "Persistent changes in neuronal structure and synaptic plasticity caused by proton irradiation." Brain Struct Funct. 2015 Mar;220(2):1161-71. Epub 2014 Jan 21. http://dx.doi.org/10.1007/s00429-014-0709-9 ; PubMed PMID: 24446074; PubMed Central PMCID: PMC4105336 , Mar-2015
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Articles in Peer-reviewed Journals	Chmielewski NN, Caressi C, Giedzinski E, Parihar VK, Limoli CL. "Contrasting the effects of proton irradiation on dendritic complexity of subiculum neurons in wild type and MCAT mice." Environ Mol Mutagen. In Press, as of November 2015. , Nov-2015
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