Fiscal Year:	FY 2015	**Task Last Updated:**	FY 10/22/2014
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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City:	Irvine	**State:**	CA
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:		**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
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
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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)		
Grant/Contract No.:	NNX13AD59G		
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 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:	We have made considerable progress in defining the extent and temporal progression of charged particle induced cognitive dysfunction in mice. Mice (6 months of age) have now been subjected to an extensive series of cognitive testing 6, 12, and 24 weeks following low dose exposure (5, 30 cGy) to 16O and 48Ti HZE ions. Behavioral tasks administered at these times reveal marked if not stunning decrements in behavior that persist 6 months following a single acute dose. Temporally coincident with these decrements are significant reductions in dendritic complexity and spine density along the very neurons that mediate neurotransmission important for the selected behavioral tasks. These measurements have also facilitated efforts at defining the relationship between individual performance and specific alterations in structural and/or synaptic integrity. When performance is calculated as a discrimination index and plotted versus spine density or synaptic puncta one can evaluate at what level these parameters translate to impaired cognition, thereby providing a quantitative criterion for risk. Thus, it appears as if HZE ion irradiation elicits significant structural deterioration of neurons that persists and contributes to the progressive dementia found long after exposure. We have also made progress in the analysis of the neurovascular niche as multiple cell types grown in conjunction in either 96-well plates or in pre-vascularized microfluidic chambers. As multiple cells types (endothelial, pericytes, mesenchymal, and neural stem) are cultured under these conditions, radiation has been found to elicit oxidative stress, and a tropism of neural stem cells migrating away from the vascularized network. These studies will be expanded in upcoming BNL campaigns to elucidate the impact of HZE ion irradiation on the interaction between neurons and the perfused vasculature. Collectively our studies have made significant strides at addressing our overarching goal aimed at determining if/how low dose charged particle irradiation elicits changes in structural and synaptic plasticity that compromise the functionality of the CNS.
Bibliography Type:	Description: (Last Updated: 04/16/2025)
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. 2014 Jan 21. [Epub ahead of print] PubMed PMID: 24446074; PubMed Central PMCID: PMC4105336 ; http://dx.doi.org/10.1007/s00429-014-0709-9 , Jan-2014
Articles in Peer-reviewed Journals	Parihar VK, Allen BD, Tran K, Chmielewski NN, Craver BM, Martirosian V, Morganti JM, Rosi S, Vlkolinsky R, Acharya M, Nelson GA, Allen AR, Limoli C. "Targeted overexpression of mitochondrial catalase prevents radiation-induced cognitive dysfunction." Antioxid Redox Signaling. 2014; Online Ahead of Print: July 29, 2014. PubMed PMID: 24949841 ; http://dx.doi.org/10.1089/ars.2014.5929 , Jul-2014