Fiscal Year:	FY 2014	**Task Last Updated:**	FY 10/08/2013
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
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No. of PhD Candidates:		**No. of Master' Degrees:**	
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No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
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Flight Program:			
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Key Personnel Changes/Previous PI:			
COI Name (Institution):	George, Steven (University of California, Irvine) Hughes, Christopher (University of California, Irvine)		
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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:	1. We have completed a comprehensive series of in vitro differentiation studies at the last 2 BNL campaigns (NSRL13A&B). Human neural stem cells (hNSCs) were cultured and triggered to differentiate over the course of 15 days. Differentiated cultures were subjected to heavy ion irradiation (16O, 28Si, 48Ti, 56Fe) using doses of 0, 5, 25, and 100 cGy at day 5 and day 10. Cultures were fixed at day 15. These fixed preparations of differentiated hNSCs are currently being analyzed for changes in differentiated markers (astroglial and neuronal), synaptic proteins (PSD-95 and synaptophysin), and micromorphometric parameters (dendritic branching and length, spine numbers and density). These studies directly address specific aim 1. 2. The experiments detailed above have been replicated in the presence of free radical scavenger N-acetyl cysteine (NAC) at 20 μM in efforts to determine whether reducing the level of radiation-induced oxidative stress would spare disruptions to neuronal anatomy. Analysis of these samples is currently underway. These studies directly address specific aim 1. 3. Log-phase cultures of multipotent human neural stem cells subjected to the irradiation conditions described above were analyzed for changes in ATP levels and the induction of an antioxidant response element containing the redox-sensitive Nrf1 and Nrf2 promoter. Cells lysates were prepared 3 and 7 days after irradiation and are being analyzed against normalized standard curves to determine whether charged particle irradiation caused changes in the antioxidant and energy profiles of hNSCs. These studies directly address specific aim 1. 4. 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 2-month old animals have now been irradiated with 16O and 48Ti ions (600 MeV) at doses of 0, 5, and 30 cGy (NSRL 12C). Animals have been analyzed for behavioral deficits at 6 and 12 weeks and will be analyzed at 24 weeks post-irradiation (pending). At 6 weeks post-IR, significant radiation-induced behavioral deficits based on novel object and place recognition have been found for both heavy ions. Behavioral data is being analyzed for the 12-week time point while data for the 24-week time point has yet to be collected. These studies directly address specific aim 3. 5. 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). These time intensive studies will continue throughout year 2. These studies directly address specific aim 3. 6. We have now successfully bred cohorts of 6-month old Tg(Thy1-EGFP)MJrs/J transgenic mice of sufficient size (n=60) for the NSRL13 campaigns. These older 6-month old mice were irradiated with 16O (600 MeV) at doses of 0, 5, and 30 cGy (NSRL 13A). Mice of this same age (6-month) will also be irradiated with 48Ti ions (600 MeV) at doses of 0, 5, and 30 cGy (upcoming NSRL 13C). Follow up studies analyzing these older mice for potential behavioral deficits and disruptions to the ultrastructural features of neurons will continue throughout the funding period. These studies directly address specific aim 3. 7. Studies relevant to specific aim 2, utilizing microfluidic chambers to grow 3D models of the neurovascular unit will be initiated in year 2, and we have received approval for 10h of beam time in the Spring of 2014 (NSRL14A) to begin this work. Publications: 1. Parihar, V.K. and Limoli, C.L. Cranial irradiation compromises neuronal architecture in the hippocampus. Proc. Natl. Acad. Sci. U.S.A. In Press (2013). Presentations: Sept. 2013 Symposia & Chair: CNS Effects of Radiation Damage, 59th Annual Meeting Radiation Research Society, New Orleans, LA. Sept. 2013 Scholars and Training workshop: The adverse effects of exposure to the space radiation environment, where in vitro and in vivo models are used to define biological responses to charged particle irradiation, 59th Annual Meeting Radiation Research Society, New Orleans, LA. June 2013 Scripps Proton Therapy Center, Causes, consequences and potential remedies for radiation injury in the CNS. San Diego, CA. Dec. 2012 NASA/ASL seminar series: Assessing radiation effects in the CNS: From the clinic to Mars and beyond. NASA Ames Research Center, Moffett Field, CA.
Bibliography Type:	Description: (Last Updated: 04/16/2025)

Articles in Peer-reviewed Journals	Parihar VK, Limoli CL. "Cranial irradiation compromises neuronal architecture in the hippocampus." Proc Natl Acad Sci U S A. 2013 Jul 30;110(31):12822-7. http://dx.doi.org/10.1073/pnas.1307301110 ; PubMed PMID: 23858442 , Jul-2013