### Project Information

- **Fiscal Year:** FY 2016
- **Task Last Updated:** FY 05/02/2016

#### Project Details

- **PI Name:** Limoli, Charles  Ph.D.
- **Project Title:** NSCOR: Mechanisms Underlying Charged Particle-Induced Disruption of CNS Function
- **Division Name:** Human Research

#### Program/Discipline

- **Program/Discipline--Element/Subdiscipline:** HUMAN RESEARCH--Radiation health

#### Human Research Program Elements

- (1) **SR:** Space Radiation

#### Human Research Program Risks

- (1) **Bmed:** Risk of Adverse Behavioral Conditions and Psychiatric Disorders
- (2) **Cancer:** Risk of Radiation Carcinogenesis
- (3) **CNS:** Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure (IRP Rev G)

#### PI Contact Information

- **PI Email:** climoli@uci.edu
- **Fax:** FY (949) 824-3566

#### Project Details

- **PI Organization Type:** UNIVERSITY
- **Organization Name:** University of California
- **PI Address 1:** Dept. of Radiation Oncology
- **PI Address 2:** Medical Sciences I, B149
- **PI Web Page:**
- **City:** Irvine
- **State:** CA
- **Zip Code:** 92697-2695
- **Congressional District:** 45

#### Comments

- **Project Type:** GROUND
- **Solicitation:** 2013-14 HERO NNJ13ZSA002N-NSCOR Radiation
- **Start Date:** 07/01/2015
- **End Date:** 06/30/2020
- **No. of Post Docs:** 1
- **No. of PhD Candidates:** 2
- **No. of Master's Candidates:** 4
- **No. of PhD Degrees:**
- **No. of Master Degrees:**
- **Monitoring Center:** NASA JSC

#### Contact Information

- **Contact Monitor:** Simonsen, Lisa
- **Contact Email:** lisa.c.simonsen@nasa.gov
- **Contact Phone:**

#### Key Personnel Changes/Previous PI

- **COI Name (Institution):** Acharya, Munjal  Ph.D. ( University of California, Irvine )
- **Bauch, Janet  Ph.D. ( University of California, Irvine )**
- **Britten, Richard  Ph.D. ( Eastern Virginia Medical School )**
- **Nelson, Gregory  Ph.D. ( Loma Linda University )**
- **Parihar, Vipan  Ph.D. ( University of California, Irvine )**
- **Soltesz, Ivan  Ph.D. ( University of California, Irvine )**
- **Vlkolinsky, Roman  Ph.D. ( Loma Linda University )**

#### Grant/Contract No.

- NNX15AI22G

#### Performance Goal No.

- **Performance Goal Text:**

---

Humans exposed to the space radiation environment encounter a different type of radiation than that found on Earth.
Humans exposed to the space radiation environment encounter a different type of radiation than that found on Earth. Highly energetic particles can traverse the body, including the brain, and leave a path of damage that is difficult to repair and disrupts function. One consequence of this exposure is the development of radiation-induced cognitive dysfunction. The focus of this application is to resolve the mechanisms leading to radiation-induced cognitive dysfunction, in order to improve risk estimates for early and late CNS (central nervous system) effects caused by exposure to the space radiation environment. We have found that radiation impacts excitatory and inhibitory circuitry in the brain differently, and leads to significant disruptions to the structural integrity of neurons while altering the levels and activity of the proteins that regulate neuronal function. The situation is further complicated by the fact that different regions of the brain exhibit differential sensitivity to charged particle irradiation. Based on the foregoing we propose a comprehensive series of mechanistic studies analyzing the biochemical, structural, and electrophysiologic changes induced by radiation exposure that alter function to impact cognition. Carefully selected cognitive tasks and a wide variety of approaches will be used to critically analyze microcircuits in the brain and how charged particle-induced changes are transmitted via unique signaling pathways between cells that can alter gene expression profiles within cells. Collectively these studies will span a radiation effects pathway from synapse to cognition, with an overarching goal of determining whether charged particle irradiation leads to alterations in the excitatory and inhibitory activity of the brain at a global and/or region specific level. Our studies will therefore elucidate the functional consequences of radiation-induced changes on cognition that impose risk on mission critical activities and long-term cognitive health.

**Scientific Overview**

The CNS NASA Specialized Center of Research (NSCOR) is organized centrally at the University of California, Irvine (UCI: PI & Director, Limoli) and is conducted between 3 other universities, including Stanford (PI and Co-director, Soltesz), Loma Linda University (LLU: PIs Nelson & Vikolinsky), and Eastern Virginia Medical School (EVMS: PI,Britten). All proposed work is focused under an overarching hypothesis that seeks to define the mechanisms contributing to charged particle–induced disruptions to CNS functionality that impact risk over acute (mission critical) and more chronic (terrestrial) timeframes. The unique composition of the NSCOR team provides the unprecedented opportunity to map a radiation effects pathway from synapse to cognition. These efforts will characterize the changes in synaptic integrity, structural parameters of neurons, electrophysiologic properties of connectivity and neurotransmission in defined circuits, and a variety of cognitive tasks that interrogate multiple cortical and hippocampal regions of the brain at various times after charged particle exposure. These studies will also be coordinated with larger field recordings of neuronal ensembles within distinct cortical regions, and with studies focused on the role of activated microglia and secreted exosomes in regulating the radiation response of the brain and how epigenetics controls the expression of key genes known to impact learning and memory. Many of the foregoing studies will be conducted in both mice and rats and all experiments will utilize males and female animals exposed at astronaut relevant ages (6 months for mice, 9 months for rats).

**Progress to date at the University of California, Irvine:**

Findings uncovered at UCI have been able to demonstrate direct links between charged particle induced disruptions to cognition and persistent damage to specific neuronal subsets interrogated by our behavioral tasks. Since our seminal paper published in Science Advances last year entitled, “What happens to your brain on the way to Mars,” we have demonstrated that these effects are even more persistent than previously thought. Significant effort has now found that rodents exposed to energetic charged particles exhibit persistent hippocampal and cortical based performance decrements using six independent behavioral tasks administered 12 and 24 weeks after irradiation. Radiation-induced impairments in spatial, episodic, and recognition memory were temporally coincident with deficits in executive function and reduced rates of fear extinction and elevated anxiety. Irradiation caused significant reductions in dendritic complexity, spine density, and altered spine morphology along medial prefrontal cortical neurons known to mediate neurotransmission interrogated by our behavioral tasks. Exposure to charged particles also disrupted synaptic integrity and increased neuroinflammation that persisted more than 6 months after exposure. These new data corroborate our prior work, and provide convincing follow up data that demonstrates why cosmic radiation encountered during deep space travel poses such a real and unique threat to the integrity of neural circuits in the brain.

**Progress to date at the Stanford University:**

Within the reporting period under this grant, work in the Soltesz lab at Stanford focused on the centrally important question of how space-relevant irradiation affects neurotransmission in the central nervous system. Recent evidence has confirmed that space relevant doses of protons can elicit persistent disruptions in cognition that can be linked to changes in the structural and synaptic plasticity of mature neurons. However, relatively little is known regarding the impact of proton exposures on circuit specific synaptic transmission and connectivity in the brain.

Results demonstrate, for the first time, that low-dose proton irradiation selectively compromises hippocampal GABAAergic inhibition, as well as local excitatory connectivity, suggesting that cell type-specific disruptions in hippocampal circuits may mechanistically contribute to radiation-induced cognitive deficits. It is noteworthy that these cell type-specific alterations both indicate an increase inhibitory drive on CA1 PCs that form the major information-processing output channels from the hippocampal formation.

**Progress to date at the Eastern Virginia Medical School:**

The initial focus of activities at this subset are to conduct complex cognitive behavioral tasks that interrogate many aspects of executive function (i.e., Attentional Set Shifting, ATSET). To date, 18 irradiated rats (6 rats/dose) and 6 sham-irradiated rats were screened for ATSET performance during February and March 2016. Overall, there were no significant differences in the ATSET performance of the irradiated rats compared to the sham-irradiated rats. However, rats that were exposed to 1.5 cGy 400 MeV/n oxygen ions took almost double the number of attempts to pass compound...
discrimination (CD) (P=0.044, Welch’s t-test). These rats have now been sent to Loma Linda University for follow up electrophysiologic assessments to uncover potential mechanisms accounting for radiation-induced deficits in CD.

Progress to date at Loma Linda University:

Infrastructure upgrades and preliminary experiments have established our ability to interrogate neocortical regions of rat brain with electrophysiological methods. We have established baseline responses to protons and oxygen ions and have observed changes in synaptic plasticity in the form of altered long-term depression. Interestingly, in rats trained for ATSET the behavioral and electrophysiologic decrements in LTD were observed in same radiation groups (0.015 Gy), but not in other groups, suggesting a correlation. Trends have been observed in AMPA-receptor mediated miniature currents in single neurons as well as changes in membrane input resistance that resembles previous results from mouse hippocampus. We are now proceeding to acquire mature male rats for a thorough characterization of proton effects in the medial prefrontal cortex and hippocampus and will investigate the properties of the perirhinal cortex as well.

Bibliography Type: Description: (Last Updated: 04/24/2019)

**Articles in Peer-reviewed Journals**


