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| **Fiscal Year:** | FY 2013 | **Task Last Updated:** | FY 06/30/2013 |
| **PI Name:** | O'Banion, Kerry M.D., Ph.D. | | |
| **Project Title:** | Local CNS and Systemic Inflammatory Effects Following Proton and Mixed Particle Exposure | | |
| **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:** | 14642-0001 | **Congressional District:** | 25 |
| **Comments:** | | | |
| **Project Type:** | Ground | **Solicitation / Funding Source:** | 2008 Space Radiobiology NNJ08ZSA001N |
| **Start Date:** | 11/01/2008 | **End Date:** | 10/31/2012 |
| **No. of Post Docs:** | 0 | **No. of PhD Degrees:** | 0 |
| **No. of PhD Candidates:** | 1 | **No. of Master' Degrees:** | 0 |
| **No. of Master's Candidates:** | 0 | **No. of Bachelor's Degrees:** | 0 |
| **No. of Bachelor's Candidates:** | 0 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Simonsen, Lisa | **Contact Phone:** | |
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| **Flight Program:** | | | |
| **Flight Assignment:** | | | |
| **Key Personnel Changes/Previous PI:** | | | |
| **COI Name (Institution):** | Finkelstein, Jacob ( University of Rochester School of Medicine )<br>Williams, Jacqueline ( University of Rochester )<br>Olschowka, John ( University of Rochester School of Medicine ) | | |
| **Grant/Contract No.:** | NNX08BA09G | | |
| **Performance Goal No.:** | | | |
| **Performance Goal Text:** | | | |

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| **Task Description:** | This proposal continues our investigation of inflammatory responses following exposure to space radiation. In particular, we will explore the effects of protons and mixed particle radiation, at doses and fluences expected during space travel, in the brain and lung as well as the systemic circulation of mice. Dose and time dependent alteration in inflammatory indices will be correlated with brain and lung degenerative changes, including failure of hippocampal neurogenesis and alterations in hippocampal dependent learning. We will also explore whether space radiation influences Alzheimer's disease pathogenesis using a unique transgenic mouse model and lung inflammation following challenge with inhaled lipopolysaccharide. Together these studies will address specific gaps in our current knowledge about the acute and late effects of space radiation on vulnerable tissues. |
| **Rationale for HRP Directed Research:** | |
| **Research Impact/Earth Benefits:** | This work provides information related to CNS effects of high energy protons. Such information may be valuable in considering proton-based radiotherapy. |
| **Task Progress:** | The principal hypothesis tested in this grant was that: Space radiation will have a dose-dependent effect on induction of local tissue and systemic inflammation that will impact hippocampal neurogenesis, behavior and degenerative disease as well as pulmonary inflammation and predisposition to subsequent pulmonary challenge.<br>This hypothesis was explored in the following four specific aims:<br><br>Aim 1. We will establish dose and time response patterns and explore interactions among inflammatory changes in brain, lung, and the systemic circulation following whole body 1000 MeV/n proton irradiation of C57BL/6 mice using the following mission-relevant doses: 200, 100, 50, 25, and 10 cGy. Similar measures will be obtained for mice exposed to mixed proton and HZE particles as well as a simulated solar particle event.<br><br>Aim 2. We will carry out analyses of hippocampal neurogenesis and hippocampal dependent and independent learning up to one year following radiation exposure and correlate changes with measures of inflammation.<br><br>Aim 3. We will determine whether space radiation exposure impacts neurodegenerative disease pathogenesis by exposing a transgenic mouse model of Alzheimer’s disease to a subset of these treatments. Specific outcomes include extent of tissue inflammation, AD-related pathology, and behavioral changes. Note that the model chosen is distinct from that being tested in the current CNS NSCOR and therefore offers a complementary means to explore this critical issue.<br><br>Aim 4. We will determine whether space radiation induced inflammation enhances the lung’s response to subsequent pulmonary challenge with lipopolysaccharide, a model of pulmonary infection.<br><br>These aims remained essentially unchanged in the course of the grant period. During this grant we conducted six separate runs at NSRL:<br><br>• Dose and time effects of protons on inflammatory indices in brain and lung (Aim 1, Experiment 1.1) and on neurogenesis and hippocampal dependent learning and memory (Aim 2, Experiment 2.1): May 4-7, 2009; NSRL Run 09A; 576 total mice used.<br><br>• Sex Differences (Experiments 1.2 and 2.2) and Mixed Particle Exposure (Experiments 1.3 and 2.3): November 17-20, 2009; NSRL Run 09C; 750 mice used.<br><br>• Proton-LPS interactions (Aim 4, Experiment 4): May 5-7, 2010; NSRL Run 10A; 150 mice used.<br><br>• HZE Effects in Alzheimer’s transgenic mice (Aim 3, Experiment 3): May 12-13, 2011; NSRL Run 11A; 75 mice used.<br><br>• Solar Flare Late Effects (Experiments 1.4 and 2.4): May 16-17, 2011; NSRL Run 11A; 150 mice used.<br><br>• Solar Flare Early Effects (added on to Experiments 1.4 and 2.4): June 25, 2012; NSRL Run 12B; 50 mice used.<br><br>We completed all experiments originally proposed in the grant and have largely completed data analyses for all aims. Although we had originally planned to carry out mRNA quantification for markers of inflammation (e.g. cytokines) in brain and lung and ELISA based measures of cytokines in blood at multiple time points, the relative lack of effects seen with inflammatory markers or behavioral outcomes at later time points reduces the rationale for carrying out these measures. However, we may elect to conduct such measures for a subset of samples in order to determine if the doses of protons used in this study show an acute systemic effect (e.g. within first 24 h).<br><br>Based on the studies conducted in this grant, the following conclusions can be made:<br><br>• Acute 1000 MeV/n proton exposure and simulated solar flare exposures at doses up to 200 cGy showed no demonstrable effects on hippocampal-dependent memory as assessed by contextual fear conditioning at times ranging from 3 to 12 months post irradiation in both male and female C57BL/6 mice irradiated at 10-12 weeks of age<br><br>• These same exposures reduced acute (within first 12 h) proliferation of adult hippocampal neural precursor cells with dose effects as low at 50 cGy for male mice and 10 cGy for female mice, but had modest or no effects on long term hippocampal neurogenesis assessed by doublecortin staining<br><br>• Neuroinflammatory changes assessed by markers of glial or endothelial activation were essentially absent in brains from mice irradiated under the conditions described above<br><br>• Addition of 10 cGy HZE irradiation (1000 MeV/n iron particles) further reduced acute neural precursor proliferation, but otherwise showed no effect in other measured indices<br><br>• There was no evidence of radiation induced late effects in lung tissue or exacerbation of inhaled LPS exposure<br><br>• APPswe/PS-1dE9 transgenic mice showed behavioral deficits and increased amyloid plaque burden following exposure to 1000 MeV/n iron particles; the later effect was observed in male mice at 9.5 months of age, 6 months post 100 cGy irradiation<br><br>We believe that these studies help to address possible thresholds underlying acute and long-term risks from space |

radiation (CNS Gaps 1 and 2), at least as related to adult hippocampal neurogenesis, and demonstrate that space radiation can enhance susceptibility to pathology associated with neurodegenerative disease (CNS Gap 3).

One caveat of our work was the choice of contextual fear conditioning for our behavioral assay. Our adoption of this approach was based on our previous experience exploring cognitive changes following neuroinflammation localized to the hippocampus and discussions with other NASA investigators, who had also adopted this approach for their work. More recent work suggests that other tasks may be more sensitive to radiation, including novel object recognition, which we did incorporate into some of our later studies. Selection of the proper tests for behavioral effects remains a major challenge, particularly with mice.

We are following up on this work with a currently funded NASA grant (NNX13AC33G) exploring the effects of HZE and proton exposure on Alzheimer's pathology in a different mouse model that demonstrates both amyloid plaques and neurofibrillary tangles. A second part of that grant will examine effects of space radiation on behavior and pathology in a genetic mouse model of Parkinson's disease. Importantly, these models show more gradual onset of disease pathology than the APP/PS1 model reported here. Therefore mice will be irradiated at 6 months of age, in accordance with guidelines to better model exposure in adulthood.

In conclusion, we have provided clear evidence of acute effects on adult hippocampal neural progenitor cells exposed to protons and enhanced Alzheimer-like pathology in a specific mouse model following HZE particle irradiation. Further studies, some of which are already in progress, will help to establish whether such changes pose a risk for space explorers.

**Bibliography Type:** Description: (Last Updated: 03/11/2025)

**Articles in Peer-reviewed Journals**

Cherry JD, Liu B, Frost JL, Lemere CA, Williams JP, Olschowka JA, O'Banion MK. "Galactic cosmic radiation leads to cognitive impairment and increased aß plaque accumulation in a mouse model of Alzheimer's disease." PLoS One. 2012;7(12):e53275. http://dx.doi.org/10.1371/journal.pone.0053275 ; PubMed PMID: 23300905 , Dec-2012