Fiscal Year:	FY 2013	**Task Last Updated:**	FY 12/04/2012
PI Name:	Vlkolinsky, Roman Ph.D.		
Project Title:	Functional decline in mice with Alzheimer's-type neurodegeneration is accelerated by charge-particle radiation		
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:	92350-1700	**Congressional District:**	41
Comments:			
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No. of Post Docs:	1	**No. of PhD Degrees:**	0
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No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date is now 1/31/2015 per NSSC information (Ed., 11/5/13)		
Key Personnel Changes/Previous PI:	Jerome Badaut, PhD ; Richard E Hartman, PhD ; Gregory Nelson, PhD ; Attila Szucs, PhD - subcontractor		
COI Name (Institution):	Nelson, Gregory (Loma Linda University) Badaut, Jerome Ph.D. (Loma Linda University) Hartman, Richard Ph.D. (Loma Linda University)		
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Performance Goal No.:			
Performance Goal Text:			
Task Description:	Exposure of an astronaut's central nervous system (CNS) to solar particle events (SPE) and galactic cosmic rays (GCR) may accelerate neurodegenerative changes and impact neuronal network activity, leading to cognitive deficits. There are similarities between radiation CNS effects and pathological processes found in the Alzheimer's disease (AD). Common functional and structural findings include profound deficits in neuronal communication (synaptic transmission), cognitive impairments, neuro-inflammatory changes and reduced neurogenesis. These similarities lead us to hypothesize that subjects with a genetic propensity to develop AD-pathology may be excessively vulnerable to ionizing radiation. We previously showed in transgenic (TG) APP23 mice, a murine model of AD, that irradiation with 600 MeV/n iron particles accelerated the onset of electrophysiological changes in the hippocampus, a brain structure crucially involved in the formation of short-term memory. In this project we use young adult APP/PSEN1?E9 (APP/PS1) double transgenic (TG) mice and expose them to low doses of 150 MeV/n proton (irradiations performed at LLU proton treatment facility), 250 MeV/n silicon and 600 MeV/n iron-particle radiation to compare and quantify their detrimental effects on hippocampal functions and the onset of AD-like pathology. The APP/PS1 TG mice typically exhibit early-onset of age-related behavioral abnormalities and deficits in synaptic transmission. We hypothesized that exposure to even low radiation doses will accelerate the onset of age-related neurodegenerative processes, while in wild-type (WT) animals such damage may stay undetectable. Comparison of proton, silicon and iron radiation on selected neurophysiological end points in APP/PS1 TG mice will provide valuable information about the risks of space radiation-induced neurodegenerative processes. The functional end points (e.g. electrophysiological and behavioral changes) will be directly correlated with the expression of immunohistochemical markers of neurodegeneration, including amyloid plaque load, synaptic proteins and expression of neuroinflammatory cytokines. This information can be directly related to risks of AD onset in human subjects.		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	While the central nervous system (CNS) has been typically described as radiation-resistant tissue, we have previous electrophysiological and new behavioral evidence showing that even low doses of ionizing radiation may affect basic neuronal processes, such as synaptic transmission, neuronal excitability and formation and consolidation of spatial memory. Specifically in the hippocampus, a brain structure intimately involved in formation of memory, the ionizing radiation has been shown to impact synaptic excitability and plasticity. In addition, it cannot be excluded that ionizing radiation, even at very low doses of 0.1-1 Gy, may promote the onset of neurodegenerative disorders that affect the hippocampus, such as the Alzheimer's disease (AD). However this hypothesis has not been fully tested with different low- and high-LET particles. Studying the impact of protons and high-LET radiation on neurodegenerative processes in mammalian CNS is a critical step, not only for the assessment of the space radiation risks for astronauts, but also for further development of modern cranial radiotherapies using charged particles. The time-dependent changes in the CNS in patients undergoing cranial irradiations have been well documented, and they range from acute mild memory deficits to severe delayed demyelination and neurodegeneration. Whether low doses of charged particle radiation may accelerate the onset or affect the severity of AD-related pathology is not known. In the current project we used a murine double transgenic model of AD that we exposed to low- and high-LET charged-particle radiation to attempt to answer this question. We test if radiation affects the time course and severity of neurodegenerative processes in these AD-prone subjects. The combination of behavioral, electrophysiological, and histological data will help us to identify functional decrements and the neurodegenerative changes in brains of the irradiated mice. The acquired data will improve our understanding of pathophysiological processes in irradiated and AD-affected CNS tissue.		

Task Progress:	Administrative Changes: In the summer of 2012 our laboratories were relocated to new premises that was associated with remodeling, transfer, and upgrade of our electrophysiological setups and supporting apparatus. This relocation was completed in June-August 2012 and did have minor impact on our irradiation/recording/data analyses schedules. Nonetheless, several technical problems and hardware related issues needed to be solved before the electrophysiological setups became fully functional and tuned for upcoming recordings. Technical Progress and Summary Results by Aims: Aim 1 & Aim 3 Activities. In accord with our statement of work (SOW), we performed 7 irradiations with protons (7 irradiation runs) in APP/PS1 transgenic (TG) and wild type mice in 2011, as described in previous task book report. Irradiations were preceded with behavioral assessments (1 week prior to irradiation) that continued at 3 and 6 months post irradiation. Ensuing in vitro electrophysiological testing was performed at 6 and 9 months post irradiation with projected start in December 2011 and end in May 2012. Due to increased mortality of APP/PS1 transgenic mice irradiated with protons in summer of 2011 (12 deaths in 66 mice), we performed an additional proton irradiation run in August of 2012 using 12 APP/PS1 TG. The electrophysiological evaluation of these mice is projecting to February 2013. Their addition was required to help to identify statistical significance in cohorts with subtle changes in synaptic plasticity. The increased mortality has not been observed in any other irradiation group. The electrophysiological experiments from the first 7 runs were completed as planned. Preliminary behavioral, electrophysiological, and histological data (see below) were presented at the NASA Space Radiation Investigators Workshop in Durham, NC, and at the Society for Neuroscience's annual conference in New Orleans, LA, 2012 (see below). The timely analyses of the functional data (e.g. the electrophysiological and behavioral tests) in these animals was critical for directing further experiments performed in APP/PS1 transgenic mice exposed to iron and silicon radiation (irradiated at Brookhaven National Laboratories in spring, summer and fall, 2012 (Aim 2)). We used conventional extracellular recordings to monitor both evoked synaptic responses and spontaneous activity. We initially implemented the multielectrode array system (MED64, Panasonic, Japan) to record excitability at multiple neuronal fields (within each brain slice) simultaneously. However, this approach proved to be highly unreliable in APP/PS1 mice due to slice instability on the chip and its susceptibility to the outside electrical noise, which precluded reliable analyses of long-term recordings of spontaneous activity. The data analyses from conventional extracellular recordings on the short-term and long-term plasticity (long-term potentiation - LTP) have been approximately 70-80% completed. These data show a trend indicating that proton radiation may impact synaptic plasticity (LTP magnitudes) in APP/PS1 TG mice. In accord with our behavioral findings (see below), in WT mice at 0.5 Gy we observed trend showing altered (increased the magnitude) of long-term synaptic plasticity at 9 months post-irradiation. The data on excitability profiles in CA1, CA3 and DG (dentate gyrus) neurons is under evaluation. The spontaneous activity recorded in CA1 and CA3 neurons reflecting memory consolidation process in the hippocampus (and known as sharp wave-ripple complexes) required the development of specialized software (by subcontractor Dr. A. Szucz, UCSD). These data are currently being analyses. Behavioral analyses of proton-irradiated animals have been completed. Data from the Morris Water maze (MWM) and the Barnes maze confirmed previously described deficits in spatial memory in APP/PS1 TG mice (increased swim distance to the target area) when compared to the WT mice. We also observed that proton radiation (0.5 Gy) affected performance of WT mice, but did not affect performance of APP/PS1 TG mice. This may indicate that low radiation may not necessarily worsen the AD-like pathology, or that such pathology trumps any radiation-induced effects. While histochemical and immunohistological evaluations were not planned for the 1st and 2nd year of the project, we started analysis of ß-amyloid deposits in brain samples (the cortex and the hippocampus) of APP/PS1 TG mice using thioflavin-S staining (fibrillar form of amyloid) and by IHC using 6E10 monoclonal antibody (Covance,Inc., NJ). Both methods confirmed amyloid depositions in brains of APP/PS1 TG mice at 6 and 9 months post irradiation at radiation dose of 1 Gy. However, no significant radiation-induced changes were observed. Analysis of radiation effects triggered by exposure to 0.1 and 0.5 Gy is underway. Aim 2 & Aim 3 Activities. In accord with our SOW, we have completed all irradiation runs at Brookhaven National Laboratories. In total, we irradiated 120 APP/PS1 transgenic mice with 600 MeV/n iron and 250 MeV/n silicon particles. Radiation doses were equivalent to those in proton-irradiated mice, which will facilitate the comparisons of radiation dose effects. After completion of irradiation runs at BNL, these animals were shipped to LLU where they have been behaviorally tested at 3 and 6 months. Due to complicated legislative issues (e.g. shipping of mice from the vendor to BNL and LLU) it was not possible to test these mice behaviorally before the radiation exposure. Three and 6 month post irradiation behavioral testing was performed identically to that of mice irradiated with protons (Aim 1). Mice were then used for electrophysiological assessments of synaptic changes at 6-7 months post irradiation. Electrophysiological testing has commenced in October of 2012 and will be completed in June of 2013. At the same time, the brain tissue (left hemisphere only) of each mouse is being processed for later histochemical and immunohistological analyses planned after June of 2013.
Bibliography Type:	Description: (Last Updated: 04/24/2019)
Abstracts for Journals and Proceedings	Rudobeck E, Mistry N, Hartman RE, Badaut J, Vlkolinsky R. "Functional Effects of Proton Radiation on Synaptic Transmission and Plasticity in the Hippocampus of APP/PSEN1 Transgenic Mice." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. Poster session: Poster #8084. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012
Abstracts for Journals and Proceedings	Bellone JA, Hartman RE, Vlkolinsky R. "Low Doses of Proton Radiation do not Induce Spatial Learning or Memory Deficits in a Mouse Model of Alzheimer's Disease." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. Poster session: Poster #8004 and oral presentation. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012
Abstracts for Journals and Proceedings	Bellone JA, Vlkolinsky R, Hartman RE. "The Effect of Low Doses of Proton Particle Radiation on Behavior in a Mouse Model of Alzheimer's Disease." Society for Neuroscience 2012, New Orleans, LA, October 13-17, 2012. Poster session: Poster #343.02. Society for Neuroscience 2012, New Orleans, LA, October 13-17, 2012. Program#/Poster#: 343.02/G11. Abstract available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=6f2594af-aa82-405b-b329-3d7d4b117591&cKey=c34ff0a5e-5059-4cd5-8935-20d2626a94ea&mKey=70007181-01c9-4de9-a0a2-eebfa14cd9f1 ; accessed 12/6/2012. , Oct-2012
Abstracts for Journals and Proceedings	Mistry M, Hartman RE, Badaut J, Mehrotra S, Vlkolinsky R. "The effect of low doses of proton particle radiation on amyloid beta deposition in a mouse model of Alzheimer's disease." Society for Neuroscience 2012, New Orleans, LA, October 13-17, 2012. Posters; F30 Poster #649.18. Society for Neuroscience 2012, New Orleans, LA, October 13-17, 2012. Program#/Poster#: 649.18/F30. Abstract available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=72dfaad9-4c6f-4063-bb71-ac72579a2e83&cKey=b2d6efb1-a577-4e5d-9316-b8ef63155176&mKey=70007181-01c9-4de9-a0a2-eebfa14cd9f1 ; accessed 12/6/2012. , Oct-2012
Awards	Bellone JA, Hartman RE, Vlkolinsky R. "John Bellone was First prize winner in student contest for 'Low Doses of Proton Radiation do not Induce Spatial Learning or Memory Deficits in a Mouse Model of Alzheimer's Disease.' 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012." Jul-2012
Awards	Bellone JA, Vlkolinsky R, Hartman RE. "John Bellone was Second Prize winner for 'Effects of Proton Radiation on Behavior in a Mouse Model of Alzheimer's Disease.' William James Excellence in Research Student Competition, LLU, October 2012." Oct-2012