Fiscal Year:	FY 2012	**Task Last Updated:**	FY 12/02/2011
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		
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Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
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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 Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
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Key Personnel Changes/Previous PI:	Jerome Badaut, PhD ; Richard E Hartman, PhD		
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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 and neuro-inflammatory changes. 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 accelerate 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 onset of AD-like pathology. The APP/PS1 mice typically exhibit early-onset of age-related behavioral abnormalities and deficits in synaptic transmission. The exposure to even low radiation doses will accelerate the onset of age-related neurodegenerative processes, while in wild-type 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 endpoints will be directly correlated with expression of immunohistochemical markers of neurodegeneration, including amyloid plaque load, synaptic proteins and the presence 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 electrophysiological evidence showing that even low doses of charged-particle ionizing radiation (2-4 Gy) may affect basic neuronal processes such as synaptic transmission, neuronal excitability and formation of memory. Specifically in the hippocampus, a brain structure intimately involved in formation of memory, the ionizing radiation has been shown to be detrimental to ongoing adult neurogenesis and to synaptic plasticity. It cannot be excluded that ionizing radiation promotes the onset of neurodegenerative disorders that affect the hippocampus, such as Alzheimer's disease (AD), however this hypothesis has not been fully tested and pathophysiological processes involved have not been characterized. In this project we use a murine double transgenic model of AD that will be exposed to charged-particle radiation. The combination of behavioral, electrophysiological, and histological data will help us to identify mechanisms of neurodegenerative changes in irradiated subjects and describe their time-course. The acquired data will not only help with assessing the radiation-related risks to astronauts, but will also improve our understanding of pathophysiological processes in the mammalian hippocampus in AD.
Task Progress:	The management of the grant at Loma Linda University (LLU) in a practical sense started with availability of funds at Loma Linda University on March 23, 2011. In order to successfully perform work on the project in its full scope two full-time positions were opened, for postdoctoral fellow and research technician, respectively. In addition, one pre-doctoral student has been involved in behavioral testing. Irradiations: From May to August 2011 we have irradiated 82 mice (66 transgenic (tg) APP/PS1 and 16 wild-type (wt) mice) with proton beam (150 MeV/n) at the age of 3 mo. Irradiations were performed according to the plan in 7 batches that were separated by 1-2 weeks. This time separation was important for the upcoming use of animals for electrophysiological experiments (6 and 9 mo later) with their rate-limiting step of 1 animal/day. Each batch contained 10-12 mice that were irradiated with 0, 0.1, 0.5 and 1.0 Gy (whole body) and they were ascribed to either 6 or 9 mo age groups. The first electrophysiological experiments will commence on December 6th, 2011. The first irradiation with iron 600 MeV/n at Brookhaven National Laboratories is scheduled in spring and summer 2012. Animal mortality: We observed increased mortality in the 1st batch of tg mice likely unrelated to irradiation, but possibly due to AD-like pathology. We plan on adding more subjects to the experimental groups to maintain the statistical power. However, if overall mortality in all cohort of animals, and specifically in batch 1 at 9 mo post-irradiation increases above 25-30%, we may need to shorten the post-irradiation interval for whole experiment from 9 mo to 6 mo. The decision will be made when first electrophysiological and histological data (specifically the thio-S staining of amyloid plaque load) become available (spring 2012) and AD-like pathology at 6 mo. will be confirmed. Behavioral testing before irradiation: In addition to our original proposal we decided to establish pre-irradiation baseline values for hippocampus-dependent behavior using the Morris Water Maze (MWM). This additional time point will promote paired-comparisons pre- vs. post-irradiation for each animal. Pre-irradiation data were recorded within 1 week after delivery of the animals to LLU. First, cued variant of MWM has been used to exclude differences in swimming ability, visual deficits, and/or motivation between APP/PS1 tg and wild-type (wt) mice, which was prerequisite for further successful behavioral testing. Next, hippocampus-dependent spatial learning (two spatial tests) was assessed in 2 consecutive days showing that wt mice performed better in spatial tasks. However, in wt mice we also observed unexpected freezing behavior that typically reflects an increased anxiety. These data require further evaluation. Up to date, all animals were tested at 3 mo. post-irradiation and batch 1 is currently undergoing behavioral testing at 6 mo post-irradiation, which will be followed with in vitro electrophysiology (Dec 6th, 2011). In addition to MWM, at 3 and 6 mo. post-irradiation, we have also included the Barnes Maze test that should strengthen our findings on spatial learning and memory deficits between irradiated groups. Technical Highlights: A new MED64 multi-electrode array setup has been assembled and will be used for measurements of spontaneous synaptic activity in the hippocampus of APP/PS1 tg mice. It has been tuned to record network activity in brain slices in vitro, in all hippocampal fields simultaneously using P5001A probes (MED64, Panasonic, Japan). At the same time conventional recordings will be performed using glass microelectrodes to assess radiation-induced changes in slice excitability that cannot be fully examined by MED64 due to limitations in stimulation currents. Our effort is currently directed towards electrophysiological recordings of spontaneous network activity, where spontaneous activity is promoted either by pharmacological manipulation of excitatory vs. inhibitory drive (e.g. blockage of GABA-ergic interneurons by bicuculline, activation of NMDA receptors by lowered extracellular magnesium or by stimulation of cholinergic inputs by physostigmine), or by electrical stimulation of afferent pathways and induction of long-term potentiation (LTP) of synaptic transmission. All these manipulations are known to promote spontaneous activity in the hippocampus and are relevant to pathological processes found in AD. These electrophysiological experiments are at their introductory phase. The first complete set of data acquired from APP/PS1 tg mice is expected to be available at the

	end of December 2011.
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