Fiscal Year:	FY 2012	**Task Last Updated:**	FY 07/31/2011
PI Name:	Wang, Huichen		
Project Title:	Molecular Basis of DNA Repair and Protection from Apoptosis in Neuronal Progenitors Exposed to Space Radiation		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:			
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:	77446	**Congressional District:**	10
Comments:	Formerly at Emory University, relocated in September 2014 (Ed., 7/7/15)		
Project Type:	Ground	**Solicitation / Funding Source:**	2008 Space Radiobiology NNJ08ZSA001N
Start Date:	10/01/2008	**End Date:**	09/30/2012
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Krzysztof, Reiss (Neurological Cancer Research, Stanley S. Scott Cancer Center, Louisiana State University Health. Sciences Center, New Orleans, LA)		
Grant/Contract No.:	NNX08BA08G		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	The health risks to astronauts exposed to space radiation include cognitive deficits and possibly accelerated aging. While the pathogenesis of radiation-induced cognitive dysfunction remains largely uncharacterized, it is thought to include loss of neural progenitors from the brain. Understanding of the molecular and cellular bases underlying neuronal loss and/or dysfunction is absolutely required for the development of counter measures before, during and possibly after space missions. Since experiments in humans are not possible, studies in this direction will benefit from appropriate biological model systems. The neurodegenerative effects of space radiation are likely to derive from DNA damage in the central nervous system (CNS). Therefore, research involving repair of this type of DNA lesions is critical for the development of new neuroprotective countermeasures. In the present proposal, we introduce an in vitro model of neural progenitors (neurospheres), which is derive from the brain of mouse embryo from neurodegenerative transgenic mice to study the detrimental effects of space radiation at the mechanistic level. Using this biological model, we will study DNA damage repair and apoptosis of proliferating and differentiated neural progenitor exposed to low dose of high charge and energy nuclei and protons. The proposed studies will provide novel insights into the molecular and cellular mechanisms underlying CNS risks from space radiation and will help to predict and countermeasure health risks from space radiation particularly with regard to effects on the CNS.		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	This proposal will study the mechanism of DNA damage and oxidative stress in neuronal cells induced by high energy particle, iron, and protons, compared to X-ray. This study will provide possible ways to develop accurate quantitative estimates to the risk of the central nervous system (CNS) from galactic cosmic ray (GCR) and solar particles events following long-term space travel.		
Task Progress:	The health and performance risks to astronauts exposed to space radiation from galactic cosmic rays (GCR) and solar particle events (SPEs) during space missions are still uncertain. Acute and late radiation damage to the central nervous system (CNS) may lead to changes in motor function and behavior, or neurological disorders. Evidence of space radiation risk to the CNS has been accumulated and reported. However, the pathogenesis of space radiation-induced cognitive dysfunction remains largely uncharacterized. The neurodegenerative effects of space radiation are likely to be derived from DNA damage in the central nervous system (CNS). In this project we used an in vitro system based on cultures of mouse embryo neuronal progenitor cells (neurospheres) to study the function of PARP-1 in the induction of clustered DNA damage after low LET an high LET radiation as well as molecular basis of DNA repair. Space radiation induced clustered DNA damage including oxidized base damage, DNA single-strand breaks and double-strand breaks were detected by a modified single cell electrophoresis, and immunodetection of 8-oxo-dG, in neurospheres and PARP-1 proficient and deficient cells. We found that Poly(ADP-ribose) Polymerase 1 (PARP-1) inhibitor induce more DNA damage in neuronal progenitor cells following 56Fe particle and proton irradiation. PARP-1 inhibition also delayed the decay of gamma H2AX foci and the residual foci associated with new replicated DNA. The level of ATM (Ataxia Telangiectasia Mutated) phosphorylations was increased in neurospheres after treatment with PARP-1 inhibitor and following irradiation. Mutation of PARP-1 in MEF cells dramatically decrease DNA damage repair. We observed that PARP-1 and PAR formed a foci track and colocalized with phosphorylated ATM and MRE11. Inhibition of Cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3 (GSK3) protect neuronal cells from high LET radiation. Here, we investigated the DNA damage complex formation and apoptosis in hippocampal neuronal cells exposed to iron particles using a novel approach to live imaging DNA damage track with fluorescent tagged DNA repair proteins (GFP-PARP-1, mCherry-53BP1 and YFP-MRE11) and live imaging caspase activity in single cell. We found that Mre11, PARP-1 and 53BP1 protein colocalized in DNA damage tracks. Less than one track was formed in each cell exposed 0.1 Gy of 56Fe (1 GeV/u) particle. Inhibition of PARP-1 reduced MRE11 track formation. This suggests that PARP-1 mediates Mre11 complex to DNA damage tracks in hippocampal neurons exposed to high LET radiation. In another study, we investigated the role of a purified component (amentoflavone) from plant extracts in radiation response in hippocampal neurons (HT22) and glioblastoma cells (U87 MG) following exposure to high linear transfer (LET) radiation and low LET radiation. We found that amentoflavone protects hippocampal neurons from radiation and enhances radiosensitivity of glioblastoma cells. Treatment of amentoflavone increased survival fractions in hippocampal neuronal cells following exposure to X-Ray radiation and 56Fe particles, though amentoflavone enhanced radiosensitivity of glioblastoma cells. Amentoflavone attenuated reactive oxygen species (ROS) and DNA damage in irradiated hippocampal neurons, and increased DNA repair activity and superoxide dismutase 1 (SOD1) expression. Pretreament of amentoflavone also increased the survival rate of mice from whole body gamma irradiation. This suggests that amentoflavone may have a potential function on cancer chemo- radiotherapy and radiation protection.		
Bibliography Type:	Description: (Last Updated: 11/13/2019)		

Abstracts for Journals and Proceedings	Tang X, Renegar J, Wang Y, Wang M, Wang C, Wang H. "PARP-1 mediate Mre11 complex to DNA damage tracks in hippocampal neurons exposed to high LET radiation." Presented at International Symposium for Radiation Research and Medical Physics, Shanghai, China, May 30-June 2, 2011. International Symposium for Radiation Research and Medical Physics, Shanghai, China, May 30-June 2, 2011, P52. , Jun-2011
Abstracts for Journals and Proceedings	Wang H, Kong X, Tang X, Zheng X, Zhu Y, Wang S, Wang H. "Effect of amentoflavone on radiation response in neuronal cells." The American Association for Cancer Research 102nd Annual Meeting, Orlando, FL, April 2-6, 2011. The American Association for Cancer Research 102nd Annual Meeting, Orlando, FL, April 2-6, 2011. Abstract #2678. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=f9b6a23d-fa6c-4796-aba8-6fc62c56cb47&cKey=310c19c5-61b7-4d58-a41c-edaadac0154e&mKey={507D311A-B6EC-436A-BD67-6D14ED39622C}, Apr-2011
Abstracts for Journals and Proceedings	Wang H, Wang Y, Kaluzova M, Tang X, Q Yin, Flemington EK, Hadjipanay C. "Effect of microRNA-155 on EGFRvIII mediated radiation response in glioblastoma tumors." The American Society for Radiation Oncology, 2011 Annual Meeting/53rd ASTRO Annual Meeting, Miami, Florida, October 2011. International Journal of Radiation Oncology * Biology * Physics. 2011 Oct;81(2 Suppl):S713. Proceedings of the 53rd Annual ASTRO Meeting. The American Society for Radiation Oncology, 2011 Annual Meeting/53rd ASTRO Annual Meeting, Miami, Florida, October 2011. http://dx.doi.org/10.1016/j.ijrobp.2011.06.1265 and click on Full Text. , Oct-2011
Awards	Wang H, Wang Y, Kaluzova M, Tang X, Q Yin, Flemington EK, Hadjipanay C. "The American Society for Radiation Oncology, 2011 Annual Meeting Scientific Abstract Award for 'Effect of microRNA-155 on EGFRvIII mediated radiation response in glioblastoma tumors.' 53rd ASTRO Annual Meeting, Miami, Florida, 2011." Oct-2011