Fiscal Year:	FY 2013	**Task Last Updated:**	FY 08/05/2012
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:**	09/30/2013
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
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date is now 9/30/2013 per NSSC information (Ed., 3/12/2013) NOTE: Extended to 3/31/2013 per NSSC information (Ed., 12/18/12)		
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:	3. Productivity of Funded NASA Research Current NASA Grant: NNX08BA08G PI: Dr. Huichen Wang Project Title: Funding period: 10/1/09 to 9/30/12 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. Cyclin-dependent kinase 5 (CDK5) is a proline-directed serine/threonine cyclin-dependent kinase in post-mitotic neurons and plays a critical role in neurogenesis. We found that the interaction of PARP-1 and CDK5 in radiation-induced DNA damage response in an in vitro system based on cultures of mouse embryo neuronal progenitor cells (neurospheres) from PARP-1 knockout mice and mouse hippocampal neuronal cells. CDK5 inhibitor (roscovitine) reversed the radiosensitivity of the PARP inhibitor in neural cells exposed to X-ray, proton and heavy ion radiation using a clonogenic survival assay. The PARP inhibitor increased radiation-induced DNA damage and apoptosis in neural cells. These effects were abrogated when the PARP inhibitor was combined with the CDK5 inhibitor. CDK5 PARP inhibitors increased radiation induced ATM expression and ATM phosphorylation in both cytoplasm and nucleus of neural cells. The GSK3 beta inhibitor also reversed radiosentitivity of neural cells. These suggest that the DNA repair pathway and the neuronal survival factors play a critical role in protecting neuronal cells following space radiation. The details of this mechanism and biological effectiveness will be discussed. Conclusion 1. We described DNA repair pathways (PARP-1 and ATM) in neural cell survival following exposure to high LET radiation. High energy particles induced larger RBE in cell survival and DNA damage of hippocampal neurons compared to X-ray radiation. PARP and ATM deficiency increased the RBE of cell survival and DNA damage induced by high charge and energy particles. Related publications: Publications/submitted manuscripts supported by NNX08BA08G 1. Wang H., Liu S., et al. (2009). "S-phase cells are more sensitive to high-linear energy transfer radiation." Int J Radiat Oncol Biol Phys 74(4): 1236-1241. 2. Cucinotta F, Wang H, Huff JL. "Risk of Acute or Late Central Nervous System Effects from Radiation Exposure." Human Health and Performance Risks of Space Exploration Missions. ed. by J.C. McPhee and J.B. Charles. Houston, Texas. NASA, 2010. p. 191-212, NASA SP 2009 3. Shi Y. Zhang X., Tang X., Wang P., Wang H., and Wang Y.MiR-21 is Continually Elevated Long-Term in the Brain after Exposure to Ionizing Radiation, Radiation Research, 177(1):124-8, 2012 4. Zhang X., Wooi-Loon N., Wang P. Tian L., Werner E., Wang H. Doetsch PW., and Wang Y. MicroRNA-21 modulates reactive oxygen species levels via targeting SOD3 and TNFa, Cancer Research, 5. Ramachandiran, S. and Wang, H., Bernal-Mizrachi L. The noncanonical NF-gammaB pathway suppresses DNA damage, centrosome amplification and chromosomal aberrations in diffuse large cell lymphomas, Leukemia, Clinical Cancer Research, revising. Manuscripts in preparation and in progression supported by NNX08BA08G

	1. Wang, M., Tian, L., Wang, H. PARP-1 is involved in clustered DNA damage in neuronal cells. In preparation. 2. Wang, M., Tian L., Wang, T., Tang X. and Wang H. Function of GSK3 in radiation induced apopotosis in neural cells, in preparation. 3. Wang Y., Tang X. Wang M. and Wang H. Amentoflavone-mediated radioprotection of hippocampal neuronal cells through reduction of ROS and DNA damage, in preparation. 4. Homologous recombination mediates persistent clustered DNA damage induced by high LET radiation, in preparation.
Bibliography Type:	Description: (Last Updated: 11/13/2019)
Abstracts for Journals and Proceedings	Kandimalla R, Wang T, Tang X, Wang H. "Interaction of APP(swe) mutant and GSK3 modulates radiation response in hippocampal neuronal cells." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. Abstract 8091. , Jul-2012
Abstracts for Journals and Proceedings	Wang T, Tang X, Wang Y, Wang C, Wang H. "Homologous recombination mediates persistent clustered DNA damage processing." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. Abstract 8090. , Jul-2012
Abstracts for Journals and Proceedings	Werner E, Tang X, Wang H, Doetsch PW. "Concurrent Delayed ROS Stress and Genomic Instability in Response to a Single Exposure to Ionizing Radiation." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. Abstract 8048. , Jul-2012
Articles in Peer-reviewed Journals	Zhang X, Ng WL, Wang P, Tian L, Werner E, Wang H, Doetsch P, Wang Y. "MicroRNA-21 modulates the levels of reactive oxygen species levels by targeting SOD3 and TNF." Cancer Research. 2012 Sep 15;72(18):4707-13. Epub 2012 Jul 25. PubMed PMID: 22836756 , Sep-2012
Articles in Peer-reviewed Journals	Shi Y, Zhang X, Tang X, Wang P, Wang H, Wang Y. "MiR-21 is continually elevated long-term in the brain after exposure to ionizing radiation." Radiat Res. 2012 Jan;177(1):124-8. Epub 2011 Oct 28. PMID: 22034847 , Jan-2012