Fiscal Year:	FY 2014	**Task Last Updated:**	FY 08/02/2013
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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City:	Prairie View	**State:**	TX
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:**	09/30/2015
No. of Post Docs:	1	**No. of PhD Degrees:**	2
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 9/30/2015 per NSSC information (Ed., 7/11/14) NOTE: End date is now 9/30/2014 per PI and NSSC information (Ed., 8/3/2013) 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:	Galactic cosmic rays (GCR) and solar particle events (SPE) include high energy and high charge (HZE) nuclei and a large amount of high energy protons. Evidence from radiobiological studies points out that HZE and protons-induced behavior change resembles the aging process, and neurogenesis causes from oxidative stress. However, the inter-relationship between oxidative stress and neurogenesis in neuronal cells remain unclear. The long term objective of this project is to investigate mechanisms of DNA damage processing in the CNS and to provide new molecular targets for countermeasure of the CNS risks from space radiation. We hypothesize that DNA repair and transcriptional regulation via the PARP-1—ATM—CREB pathway play a pivotal role in neuronal defense responses to neurodegenerative effect of HZE and protons. Task progress: In this year, we performed the following studies: 1. Live imaging DNA damage process in neuronal cells following exposure to 0.1- 1Gy of 56Fe(1 GeV) and proton (1 GeV). We found that HZE particle induced persistent DNA damage in neuronal cells. This DNA damage signaling may transit to progeny cells. 2. Detection of effect of poly(ADP-ribose) polymerase 1 in DNA damage response in neuronal cells. We found that PARP-1 dependent DNA repair pathway is involved in clustered DNA damage repair in neuronal cells following exposure HZE particles. 3. Detection of the effect of glycogen synthase kinase 3 on radiation response in neuronal cells. We found that inhibition of GSK3 protect neuronal cells from space radiation. 4. Study on the effect of HZE on the processing of Amyloid precusor proteins in neuronal cells. 56Fe(1GeV) induces cleavage of APP c-terminal and translocation to nuclear in neuronal cells. 5. Study on High LET radiation produces sustained DNA damage signaling and changes cellular homeostasis in hippocampal neuronal cells. 1 Gy 56Fe(1GeV) induced persistent increased p53 expression and camp response element binding protein phosphorylation. The results are described in published papers, and presented as abstracts in the following list and in several manuscripts. Manuscripts supported by NNX08BA08G 1. Wang, T., Wang, M., Tian, L., Wang, H. PARP-1 is involved in clustered DNA damage in neuronal cells. Pols one revised 2. Ramachandiran, S. and Wang, H., Bernal-Mizrachi L. The noncanonical NF-kB pathway suppresses DNA damage, centrosome amplification and chromosomal aberrations in diffuse large cell lymphomas, Leukemia, Clinical Cancer Research, revising. 3. Wang, M., Tian L., Wang, T., Tang X. and Wang H. Function of GSK3 in radiation induced apopotosis in neural cells, in preparation. 4. Li Z, Hudson FZ, Wang H, Wang Y, Bian Z, Murnane JP, Dynan WS "Increased mutagenic joining of enzymatically-induced DNA double-strand breaks in high-charge and energy particle irradiated human cells" Radiat Res. 2013 Jul;180(1):17-24 PMID: 23692479 , May-2013 Abstracts in professional meeting 1. Wang T Kandimalla R, , Tang X, Wang H APP intracellular domain increases DNA damage response in hippocampal neuronal cells following exposure to high LET radiation Heavy ion in therapy and space radiation symposium , 24th Annual NASA Space Radiation Investigators' Workshop, Chiba, Japan, May 15-18 2013 2. Wang T, Kandimalla R, Tang X, Wang H High LET radiation produces sustained DNA damage signaling and changes cellular homeostasis in hippocampal neuronal cells Heavy ion in therapy and space radiation symposium , 24th Annual NASA Space Radiation Investigators' Workshop, Chiba, Japan, May 15-18 2013 3. Werner E, Kandimalla R, Wang H, and Doetsch PW, A role for reactive oxgen species in the resolution of persistent genomic instability after exposure to radiation Heavy ion in therapy and space radiation symposium , 24th Annual NASA Space Radiation Investigators' Workshop, Chiba, Japan, May 15-18 2013 4. Werner E, Kandimalla R, Wang H, and Doetsch PW. Early and persistent effect of PARP inhibition after exposure to radiation Heavy ion in therapy and space radiation symposium, 24th Annual NASA Space Radiation Investigators' Workshop, Chiba, Japan, May 15-18 2013

	5. Li Z, Hudson FZ, Wang H, Murane JP, Dynan Ws. Secretoty protein phenotypes accompanied by mutagenic joining of enzymatically-induced DNA double-strand breaks in a population of HZE-exposed human cells. Heavy ion in therapy and space radiation symposium, 24th Annual NASA Space Radiation Investigators' Workshop, Chiba, Japan, May 15-18 2013
Bibliography Type:	Description: (Last Updated: 11/13/2019)
Abstracts for Journals and Proceedings	Wang T, Kandimalla R, Tang X, Wang H. "APP intracellular domain increases DNA damage response in hippocampal neuronal cells following exposure to high LET radiation." CNS risk. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. , May-2013
Abstracts for Journals and Proceedings	Wang T, Kandimalla R, Tang X, Wang H. "High LET radiation produces sustained DNA damage signaling and changes cellular homeostasis in hippocampal neuronal cells." CNS risk. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. , May-2013
Abstracts for Journals and Proceedings	Werner E, Kandimalla R, Wang H, Doetsch PW. "A role for reactive oxgen species in the resolution of persistent genomic instability after exposure to radiation." Carcinogenesis risk. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. , May-2013
Abstracts for Journals and Proceedings	Werner E, Kandimalla R, Wang H, Doetsch PW. "Early and persistent effect of PARP inhibition after exposure to radiation." 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. 24th Annual NASA Space Radiation Investigators' Workshop. HITSRS2013--Heavy Ion in Therapy and Space Radiation Symposium 2013, Chiba, Japan, May 15-18, 2013. , May-2013
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Articles in Peer-reviewed Journals	Li Z, Hudson FZ, Wang H, Wang Y, Bian Z, Murnane JP, Dynan WS. "Increased mutagenic joining of enzymatically-induced DNA double-strand breaks in high-charge and energy particle irradiated human cells." Radiat Res. 2013 Jul;180(1):17-24. http://dx.doi.org/10.1667/RR3332.1 ; PubMed PMID: 23692479 , Jul-2013