Fiscal Year:	FY 2013	**Task Last Updated:**	FY 10/31/2012
PI Name:	Li, Chuan-Yuan Ph.D.		
Project Title:	A mechanistic investigation of space radiation-induced carcinogenesis		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation Biology		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	chuan.li@duke.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	919 613 8754
Organization Name:	Duke University		
PI Address 1:	Box 3135, DUMC C303A/LSRC		
PI Address 2:			
PI Web Page:			
City:	Durham	**State:**	NC
Zip Code:	27710	**Congressional District:**	4
Comments:	PI moved to Duke University in December 2011. Formerly at University of Colorado Denver (Ed., 2/8/2012)		
Project Type:	Ground	**Solicitation / Funding Source:**	2008 Space Radiobiology NNJ08ZSA001N
Start Date:	01/01/2012	**End Date:**	10/31/2013
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA ARC
Contact Monitor:	Griko, Yuri	**Contact Phone:**	650-604-0519
Contact Email:	Yuri.V.Griko@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: to be extended to 10/31/2013 per A. Chu/ARC and NSSC information (Ed., 11/1/2012)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Li, Fang (Duke University)		
Grant/Contract No.:	NNX12AB88G		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	One of major concerns for manned space missions of NASA is exposure to galactic cosmic rays (GCRs) or highly charged energetic (HZE) particles, which carries distinct health risks. The major goal of the NASA Bioastroanautics Roadmap and NASA ground-based studies in radiation biology is to assess potential risks of human exposure to HZE particles and to generate knowledge that can be used to mitigate the health risks of HZE particle exposure eventually. In this project, we will two specific aims to study HZE particle-induced mutagenesis and carcinogenesis in mammalian cells. These are: 1. To determine the potential interactions of reactive oxygen/nitrogen species and apoptosis in regulating HZE radiation-induced mutagenesis in mammalian cells. 2) to determine the roles of program cell death in HZE radiation induced mutagenesis/carcinogenesis.		

Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research will have the following potential benefit for life on Earth: 1) we will develop state-of-art techniques to monitor radiation induced DNA damage, which will facility a better understanding radiation induced carcinogenesis in humans. 2) our study may lead to fundamental insights into how cells deal with DNA damage. 3) we hope to achieve novel, mechanistic insights into the carcinogenic risks of radiation, which is universally present on Earth.
Task Progress:	Our current grant, NNX12AB88G, is a transfer grant from University of Colorado Denver to Duke University. This is a result of the PI's moving from the University of Colorado to Duke. The major goals of this project are to understand the roles of free radicals and programmed cell death in space radiation induced mutagenesis and carcinogenesis. Towards these goals, we have made major progress in the funding period. Major achievements include: A). The development of a non-invasive bioluminescence-based imaging method to monitor gamma H2AX foci, a major indicator of DNA double strand breaks (DSBs) (Li et al., Cancer Research, 2011, 71:4130-7). Using this reporter, we showed that space radiation induced DSBs came in two waves. The first wave occurs within minutes and lasted for hours while the second wave occurs after 24 hrs and lasted for more than a week. The second wave of DNA damage has strong implications for space radiation induced DNA damage and carcinogenesis. This type of damage could be responsible for persistent genetic instability often observed after radiation exposure. B). The discovery of the "Phoenix Rising" pathway for wound healing and tissue regeneration. We discovered that dying cells in damaged tissues play a key role in mediating wound healing and tissue regeneration (Li et al., Science Signaling, 2010, 3:110: ra3) Surprisingly, caspase 3 and caspase 7, which are usually recognized as executioners of damaged or unwanted cells, play key facilitative roles regulating growth-promoting signals from dying cells. The elucidation of the counter-intuitive roles of apoptotic cells and apoptotic caspases significantly advanced our understanding of tissue homeostasis mechanisms in metazoan organisms. C). We also found that the same "Phoenix Rising" pathway was hijacked by tumors during radiotherapy. Dying cells in tumors exposed to radiation release potent caspase 3-controlled growth signals that promote the growth of surviving tumor cells, which fuels the repopulation of damaged tumor. Most importantly, consistent with these findings, higher levels of activated caspase 3 in tumor samples from human patients correlated with worse prognosis. These results are counter-intuitive and significantly changed the way we view cell death during tumor radiotherapy. D). Another discovery that we made concerns with surprising roles of caspases 3&8 in epigenetic reprogramming. We show that during induction of induced pluripotent stem (iPS) cells from human and mouse fibroblasts, caspases 3 and 8 are clearly activated. However, contrary to conventional wisdom, we found that blocking caspase activation did not increase the efficiency of iPSC induction. Instead, it significantly attenuated or completely blocked iPSC induction (Li et al., Cell Stem Cell, 2010, 7:508-20). These findings suggest that capases played a facilitative role for epigenetic reprogramming, a role that has not been suggested before. Our paper was the cover story for Cell Stem Cell. This finding may have significant implications for space radiation and other forms of carcinogenesis. E). Still another significant finding in the funding period of this project involves the successful reprogramming of primary human fibroblasts into dopaminergic neurons (Liu et al,, Cell Research, 22:321-332). We showed that a combination of 5 transcription factors (Mash1, Ngn2, Sox2, Nurr1, and Pitx3) can directly reprogram human primary fibroblasts into doparminergic neurons. These cells should stimulate research in providing a promising autologous source for cell replacement therapy for Parkinson's disease. In addition to the above accomplishments, we have now focused our attention on the roles of caspases on space radiation induced carcinogenesis and mutagenesis. We have obtained preliminary evidence that caspase 3 activation plays a key role in mediating space radiation induced carcinogenesis and mutagenesis. In the remaining time of our grant (under request for no-cost extension), we will focus our attention on obtaining sufficient data to publish this very important new finding.
Bibliography Type:	Description: (Last Updated: 10/30/2019)
Articles in Peer-reviewed Journals	Brogan J, Li F, Li W, He Z, Huang Q, Li C-Y. "Imaging molecular pathways: reporter genes." Radiation Research. 2012 Apr;177(4):508-13. Epub 2012 Feb 21. Review. PubMed PMID: 22348248 , Apr-2012
Articles in Peer-reviewed Journals	Kon T, Zhang X, Huang Q, Yang Z, Liu S, Yan B, Li F, Wang H, Li C-Y. "Oncolytic virus-mediated tumor radiosensitization in mice through DNA-PKcs-specific shRNA " Translational Cancer Research. 2012 Jun;1(1):6-14. PMID: 22924158 ; http://dx.doi.org/10.3978/j.issn.2218-676X.2012.05.02 , Jun-2012
Journal/Magazine covers	Kon T, Zhang X, Huang Q, Yang Z, Liu S, Yan B, Li F, Wang H, Li CY. "Cover in first issue of the journal Translational Cancer Research for article, Oncolytic virus-mediated tumor radiosensitization in mice through DNA-PKcs-specific shRNA." Translational Cancer Research. 2012 Jun;1(1):6-14. http://dx.doi.org/10.3978/j.issn.2218-676X.2012.05.02 , Jun-2012