

<b>Fiscal Year:</b>	FY 2014	<b>Task Last Updated:</b>	FY 02/12/2014
<b>PI Name:</b>	Li, Chuan-Yuan Ph.D.		
<b>Project Title:</b>	A mechanistic investigation of space radiation-induced carcinogenesis		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	HUMAN RESEARCH		
<b>Program/Discipline--Element/Subdiscipline:</b>	HUMAN RESEARCH--Radiation Biology		
<b>Joint Agency Name:</b>		<b>TechPort:</b>	No
<b>Human Research Program Elements:</b>	(1) <b>SR</b> :Space Radiation		
<b>Human Research Program Risks:</b>	(1) <b>Cancer</b> :Risk of Radiation Carcinogenesis		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
<b>PI Email:</b>	<a href="mailto:chuan.li@duke.edu">chuan.li@duke.edu</a>	<b>Fax:</b>	FY
<b>PI Organization Type:</b>	UNIVERSITY	<b>Phone:</b>	919 613 8754
<b>Organization Name:</b>	Duke University		
<b>PI Address 1:</b>	Box 3135, DUMC C303A/LSRC		
<b>PI Address 2:</b>			
<b>PI Web Page:</b>			
<b>City:</b>	Durham	<b>State:</b>	NC
<b>Zip Code:</b>	27710	<b>Congressional District:</b>	4
<b>Comments:</b>	PI moved to Duke University in December 2011. Formerly at University of Colorado Denver (Ed., 2/8/2012)		
<b>Project Type:</b>	Ground	<b>Solicitation / Funding Source:</b>	2008 Space Radiobiology NNJ08ZSA001N
<b>Start Date:</b>	01/01/2012	<b>End Date:</b>	10/31/2013
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	
<b>No. of PhD Candidates:</b>		<b>No. of Master' Degrees:</b>	
<b>No. of Master's Candidates:</b>		<b>No. of Bachelor's Degrees:</b>	
<b>No. of Bachelor's Candidates:</b>	1	<b>Monitoring Center:</b>	NASA ARC
<b>Contact Monitor:</b>	Griko, Yuri	<b>Contact Phone:</b>	650-604-0519
<b>Contact Email:</b>	<a href="mailto:Yuri.V.Griko@nasa.gov">Yuri.V.Griko@nasa.gov</a>		
<b>Flight Program:</b>			
<b>Flight Assignment:</b>	NOTE: Extended to 10/31/2013 per A. Chu/ARC and NSSC information (Ed., 11/1/2012)		
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Li, Fang ( Duke University )		
<b>Grant/Contract No.:</b>	NNX12AB88G		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			
<b>Task Description:</b>	<p>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 Bioastronautics 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, our two original specific aims focused on the study of 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. Later, after approval from NASA program manager, we have re-focused our efforts to some extent to study the effect of apoptotic caspases on the space radiation</p>		

	induced mutagenesis and carcinogenesis.
<b>Rationale for HRP Directed Research:</b>	
<b>Research Impact/Earth Benefits:</b>	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.
<b>Task Progress:</b>	<p>This grant was initially awarded when the PI was at the University of Colorado School of Medicine. Part of funds that were unspent were transferred to Duke University where the PI moved in 2011. Despite the move, the major focus of the project remained the same: to carry out mechanistic investigations of space radiation-induced mutagenesis and carcinogenesis. Towards these goals, we have made a substantial amount of progress in the funding period. Major achievements include:</p> <p>A). The development of a non-invasive bioluminescence-based imaging method to monitor gammaH2AX 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.</p> <p>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.</p> <p>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.</p> <p>D). Another discovery that we made concerns with surprising roles of caspases 3&amp;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.</p> <p>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, 22:321-32). We showed that a combination of 5 transcription factors (Mash1, Ngn2, Sox2, Nurr1, and Pitx3) can directly reprogram human primary fibroblasts into dopaminergic neurons. These cells should stimulate research in providing a promising autologous source for cell replacement therapy for Parkinson’s disease.</p> <p>F). We have also discovered a counter-intuitive role for caspase 3 in facilitating space radiation induced DNA damage and carcinogenesis. Instead of acting as a tumor suppressor, which is the prevalent current thinking, we found strong evidence indicating that caspase 3 is causing additional damage is cells that survived the radiation insult. We are currently working hard to publish our results. A manuscript on these findings is now being considered by the journal Cell.</p>
<b>Bibliography Type:</b>	Description: (Last Updated: 10/30/2019)
Articles in Peer-reviewed Journals	Ng WL, Huang Q, Liu X, Zimmerman M, Li F, Li CY. "Molecular mechanisms involved in tumor repopulation after radiotherapy." Translational Cancer Research. 2013 Oct;2(5):442-8. <a href="http://dx.doi.org/10.3978/j.issn.2218-676X.2013.10.03">http://dx.doi.org/10.3978/j.issn.2218-676X.2013.10.03</a> , Oct-2013
Articles in Peer-reviewed Journals	Zimmerman MA, Huang Q, Li F, Liu X, Li CY. "Cell death-stimulated cell proliferation: a tissue regeneration mechanism usurped by tumors during radiotherapy." Semin Radiat Oncol. 2013 Oct;23(4):288-95. <a href="http://dx.doi.org/10.1016/j.semradonc.2013.05.003">http://dx.doi.org/10.1016/j.semradonc.2013.05.003</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/24012343/">PMID: 24012343</a> , Oct-2013
Articles in Peer-reviewed Journals	Liu X, He Y, Li F, Huang Q, Kato TA, Hall RP, Li CY. "Redefining the roles of apoptotic factors in carcinogenesis." Mol Cell Oncol. 2016 May;3(3): e1054550. <a href="https://doi.org/10.1080/23723556.2015.1054550">https://doi.org/10.1080/23723556.2015.1054550</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/27314073/">PMID: 27314073</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC4909400/">PMCID: PMC4909400</a> , May-2016
Articles in Peer-reviewed Journals	Liu X, He Y, Li F, Huang Q, Kato TA, Hall RP, Li CY. "Caspase-3 promotes genetic instability and carcinogenesis." Mol Cell. 2015 Apr 16;58(2):284-96. Epub 2015 Apr 9. <a href="https://doi.org/10.1016/j.molcel.2015.03.003">https://doi.org/10.1016/j.molcel.2015.03.003</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/25866249/">PMID: 25866249</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC4408780/">PMCID: PMC4408780</a> , Apr-2015