Fiscal Year:	FY 2023	**Task Last Updated:**	FY 10/31/2022
PI Name:	Shay, Jerry W. Ph.D.		
Project Title:	Mouse Models of Cancer Risk and Prevention from Space Radiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
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:	jerry.shay@utsouthwestern.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	214-648-3282
Organization Name:	University of Texas Southwestern Medical Center		
PI Address 1:	Cell Biology Department		
PI Address 2:	5323 Harry Hines Blvd		
PI Web Page:			
City:	Dallas	**State:**	TX
Zip Code:	75390-7208	**Congressional District:**	30
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
Start Date:	01/29/2016	**End Date:**	12/31/2023
No. of Post Docs:	2	**No. of PhD Degrees:**	1
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Elgart, Robin	**Contact Phone:**	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/31/2023 per NSSC information (Ed., 11/14/22) NOTE: End date changed to 9/30/2022 per L. Barnes-Moten/JSC (Ed., 3/30/21) NOTE: End date changed to 1/28/2021 per NSSC information (Ed., 2/21/2020)		
Key Personnel Changes/Previous PI:	November 2020 report: Silvia Siteni, PhD postdoctoral trainee; Krishna Luitel (completed PhD) now a postdoctoral trainee.		
COI Name (Institution):			
Grant/Contract No.:	NNX16AE08G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Overall hypothesis: Low-dose radiation induces molecular manifestations of a pro-inflammatory response as a function of radiation type, radiation doses, doses rates, LET (linear energy transfer) value, and time. An oral available anti-inflammatory countermeasure, already in human clinical trials with a good safety profile, will significantly reduce proton and HZE-ion (high charge energy-ion) exposure associated tumor initiation and progression. The overarching hypothesis for this project is that space radiation induces molecular manifestations of a pro-inflammatory response as a function of radiation type, radiation doses, doses rates, LET value, and time. We are testing if an oral available anti-oxidant and anti-inflammatory countermeasure, already in human clinical trials with a good safety profile, CDDO, significantly reduces proton and HZE-ion exposure associated tumor initiation and progression. Based on experiments conducted at the NASA Space Radiation Laboratory (Brookhaven, NY) we demonstrate that HZE ion components of GCR (galactic cosmic radiation) result in persistent DNA damage and inflammatory signaling, increased mutations in tumor suppressor genes, and higher rates of cancer initiation and progression compared to that seen with similar doses of terrestrial radiation. While physical shielding may reduce some of the risks of space radiation, there is substantial evidence that biological countermeasures will be required to ensure that the established safety limits of increased lifetime fatal cancer risks are not exceeded. We are conducting GCR simulations consisting of fast switching between protons, helium, and silicon using a dose rate of 0.5 cGy/min and a total combined dose of between 27-30 cGy to more closely mimic the space environment on a trip to Mars and back. Finally, we are conducting experiments with the official NASA GCRsim with acute and protracted mixed fields. References Kim, S.B., Bozeman, R.G., Kaisani, A., Kim, W., Zhang, L., Richardson, J.A., Wright, W.E., and Shay, J.W. Radiation promotes colorectal cancer initiation and progression by inducing senescence-associated inflammatory responses. Oncogene. 2015. https:// Norbury, J.W., Schimmerling, W., Slaba, T.C., Edouard Azzam, Francis F. Badavi, Giorgio Baiocco, Eric Benton, Veronica Bindi, Eleanor A. Blakely, Steve R. Blattnig, David A. Boothman, Thomas B. Borak, Richard A. Britten, Stan Curtis, Michael Dingfelder, Marco Durante, William Dynan, Amelia Eisch, S. Robin Elgart, Dudley T. Goodhead, Peter M. Guida, Lawrence H. Heilbronn, Christine E. Hellweg, Janice L. Huff, Amy Kronenberg, Chiara La Tessa, Derek Lowenstein, Jack Miller, Taksahi Morita, Livio Narici, Gregory A. Nelson, Ryan B. Norman, Takeo Ohnishi, Andrea Ottolenghi, Zarana S. Patel, Guenther Reitz, Adam Rusek, Ann-Sofie Schreurs, Lisa A. Scott-Carnell, Edward Semones, Jerry W. Shay, Vyacheslav A. Shurshakov, Lembit Sihver, Lisa C. Simonsen, Michael Story, Mitchell S. Turker, Yukio Uchihori, Jacqueline Williams, Cary J. Zeitlin. Galactic cosmic ray simulation at the NASA Space Radiation Laboratory. Life Sciences in Space Research 8:38-51, 2016. PMID: 26948012 Lutiel, K. Bozeman, R., Kaisani, A. Kim, S.B., Barron, S., Richardson, J.A., Shay, J.W. Proton radiation-induced cancer progression. Life Sciences in Space Research, 2018. https:// Luitel, K., Kim, S.B., Barron, S. Richardson, J.A. and Shay, J.W. Lung cancer progression using fast switching multiple ion beam irradiation and countermeasure prevention, Life Sciences in Space Research, 2019. https://
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Although radiation therapy is commonly used for treatment of many human diseases, including cancer, ionizing radiation produces reactive oxygen species that can damage both cancer and healthy cells in tissues. We have demonstrated using the biological countermeasure, CDDO, an anti-oxidant, anti-inflammatory modulator with a known mechanism of action, a reduction in both cancer initiation and progression in mouse models after exposure to either terrestrial or space radiation. We also demonstrated that CDDO can be used as a radioprotector in normal non cancerous human lung and breast epithelial cells exposed to space and terrestrial irradiations while cancer cells were not protected. This suggests the use of this oral available, non-toxic class of drug can protect non-cancerous healthy cells during radiotherapy, resulting in better outcomes with less toxicity for patients. CDDO is currently in a phase 3 clinical trial for patients with pulmonary arterial hypertension and Alport's syndrome. In preliminary experiments aspirin did not provide this protection. Other potential countermeasures such as metformin continue to be tested and show radioprotective activity. In the future, CDDO or metformin may be used to protect astronauts on long-term mission to Mars as well as patients receiving radiotherapy on Earth. These radioprotectors may also have utility in protecting first responders to nuclear accidents.
Task Progress:	Per the Principal Investigator (PI): This project was initiated January 27, 2016 and is currently in a no cost extension due to some delays associated with the COVID-19 pandemic. Our team participated in almost all NASA Space Radiation Laboratory (NSRL) runs during the grant period, except during the pandemic, but due to help from the Brookhaven National Laboratory (BNL) team, progress continued during the initial no cost extension (NCE) period. (Ed., 12/8/22). Using a mouse model of lung cancer, we have tested the 33 beam GCRsim in a range of doses from 25 to 100 cGy. Mice were exposed to GCRsim and one year later sacrificed to examine for advanced lung and other cancers. At doses below 75cGy we did not observe an increase in advanced cancers. However, at 75cGy provided acutely (over 2 hours) or protracted (over 6 weeks) we did observe a significance increase in the appearance of invasive cancers. We next tested CDDO and metformin as a radioprotector and experiments are ongoing.
Bibliography Type:	Description: (Last Updated: 02/21/2024)