

Fiscal Year:	FY 2024	Task Last Updated:	FY 01/30/2024
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		
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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:	
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
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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:

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**Task Description:**

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://doi.org/10.1038/ng.3258>

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](https://doi.org/10.1016/j.lssr.2016.05.002)

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://doi.org/10.1016/j.lssr.2018.05.002>

Lutiel, 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://doi.org/10.1016/j.lssr.2019.05.002>

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 has been recently approved by the FDA to treat patients with Friedreich's ataxia. 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 the Moon or Mars as well as patients receiving radiotherapy on Earth. These radioprotectors may also have utility in protecting first responders to nuclear accidents.

Research conducted at the NASA Space Radiation Laboratory (Brookhaven, NY) demonstrated that HZE ion components of the galactic cosmic radiation (GCR) result in persistent inflammatory signaling [1-2], increased mutations, and higher rates of cancer initiation and progression [3-5] compared to that seen with terrestrial radiation. Most previous charged particle radiation studies have been performed using mono-energetic single ion or fast switching several ions radiation exposures, but the deep space environment is composed of multiple ions with a wide range of energies. Experiments were conducted to more closely simulate the deep space environment with the high energy and control upgrades at the NASA Space Radiation Laboratory. The delivery dose consists of 33 ions with different energies mixed, approximating the deep space environment. Using these upgrades, we performed acute exposure experiments lasting 1-2 hours (25cGy-100cGy), and chronic/protracted exposure experiments up to 4-6 weeks with a total dose of 50cGy and 75cGy. We obtained histological samples from a subset of mice 100 days post-irradiation, and the remainder of the mice were maintained for overall survival ending 1-year, post-irradiation. With the acute exposure of 25cGy, we did not see any increase in adenocarcinoma nor a decrease in median survival days. With the acute exposure of 100cGy, we observed a two-fold increase in adenocarcinoma and a decrease in median survival. When we compared acute exposures (1-2 hrs.) and chronic exposure (4-6 weeks), we found a statistically significant increase of adenocarcinoma for chronic exposure (6 weeks) to 75cGy GCRsim, and found a non-statistical trend in the increase of adenocarcinoma for acute exposure (2 hrs.) of 75cGy GCRsim. Additionally, there is a non-statistical trend in the increase of adenocarcinoma acute exposures (1.5 hrs.) and chronic exposure (4 weeks) of 50cGy GCRsim. Furthermore, when we added 10cGy neutron exposure to the 75cGy acute GCRsim, we observed an increase in the incidence of adenocarcinoma. We interpret these findings to suggest that the risks of carcinogenesis are heightened with doses anticipated during a round trip to Mars, and this risk is magnified when coupled with extra neutron exposures that are expected on the Martian surface. We also observed that risks are reduced when the NASA official 33-beam GCR simulations are provided at high dose rates compared to low dose rates. Overall, these experiments can be interpreted to suggest that biological countermeasures may be required on long-term space missions where astronauts will be exposed to these doses of GCR in addition to neutron exposures on the Moon and Mars.

Task Progress:

[1] Kim SB, Bozeman RG, Kaisani A, Kim W, Zhang L, Richardson JA, Wright WE, Shay JW. *Oncogene*. 2016 Jun

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Bibliography Type:	Description: (Last Updated: 02/21/2024)
Articles in Peer-reviewed Journals	Luitel K, Siteni S, Barron S, Shay JW. "Simulated galactic cosmic radiation-induced cancer progression in mice." Life Sciences in Space Research. 2024 Feb 1. Online ahead of print. https://doi.org/10.1016/j.lssr.2024.01.008 , Feb-2024
Articles in Peer-reviewed Journals	Huff JL, Poignant F, Rahmanian S, Khan N, Blakely EA, Britten RA, Chang P, Fornace AJ, Hada M, Kronenberg A, Norman RB, Patel ZS, Shay JW, Weil MM, Simonsen LC, Slaba TC. "Galactic cosmic ray simulation at the NASA Space Radiation Laboratory--Progress, challenges and recommendations on mixed-field effects." Life Sci Space Res. 2023 Feb;36:90-104. https://doi.org/10.1016/j.lssr.2022.09.001 ; PMID: 36682835 , Feb-2023