

Fiscal Year:	FY 2020	Task Last Updated:	FY 11/16/2019
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		
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Space Biology Special Category:	None		
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Comments:			
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Flight Program:			
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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://>

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://pubmed.ncbi.nlm.nih.gov/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://>

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. DOI: 10.1016/j.lssr.2019.07.011

Rationale for HRP Directed Research:

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 are now being tested. In the future, CDDO may be used to protect astronauts on long-term mission to Mars as well as patients receiving radiotherapy on Earth. This radioprotector may also have utility in protecting first responders to nuclear accidents.

Research Impact/Earth Benefits:

Our previous experiments conducted at the NASA Space Radiation Laboratory (Brookhaven, NY) demonstrated that HZE ion components of the GCR result in persistent inflammatory signaling, increased mutations, and higher rates of cancer initiation and progression compared to that seen with terrestrial radiation. Most charged particle radiation studies until recently have been performed using mono-energetic single ion radiation exposures, but the deep space environment is composed of multiple ions with a wide range of energies.

During the current reporting period, using the fast beam switching technology developed in the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), we used mixed ions with different energies to simulate the space environment. Previously, we exposed a lung cancer susceptible mouse model (K-rasLA-1) at the NSRL with three ion beams: Protons (H) (120 MeV/n) 20cGy, Helium (He) (250 MeV/n) 5 cGy, and Silicon (Si) (300MeV/n) 5cGy with a dose rate of 0.5 cGy/min. In our recent studies we observed increases in the incidence of lung cancer initiation and progression. Additionally, when we titrated the dose of HZE ion, we observed a dose-dependent effect of silicon ions delivered. Overall, we observed reducing the total dose of silicon from 5 cGy to 2 cGy and 0.5 cGy in combination with 20 cGy protons and 5 cGy of helium, reduced cancer progression back to background rates.

With the high energy and control upgrades at the NSRL, experiments are now being conducted to better simulate the deep space environment with low fluence rates predominated by low background fluences of low-LET radiation with lower fluences of high-LET radiation. These experiments consist of chronic exposure from 2-6 weeks irradiation (6-days per week) or acute one-day exposures with continuous exposure to background protons and helium and a sporadic heavy ion exposure. The delivery dose consists of 33 ions and energy mix to even more closely approximate the deep space environment. During NSRL18B and NSRL19A an acute 0.5 Gy and 0.75 Gy total exposure to the newly developed GCR simulation was initiated and first results from this acute exposure GCR simulation are currently being analyzed. During NSRL18C a chronic/protracted (4 week exposure) 0.5 Gy total exposure was performed to better simulate the low dose rates expected in the deep space environment, and results from these experiments are being finalized and results will be forthcoming.

<p>Task Progress:</p>	<p>We are also currently (NSRL19C) irradiating mice with a chronic/protracted (6 weeks exposure) 0.75 Gy total exposure. These results will be compared to the acute 0.75 Gy experimental results of NSRL19A. While we will obtain some initial results at 100 day post IR, we need to retain the mice for one year post IR to determine if there is an increase in more advanced (invasive) cancer associated with the GCR simulations.</p> <p>We continue our experiments on medical countermeasures that may reduce effects of GCR simulations associated cancers. For long-term space missions to the Moon or Mars, it might be necessary to adopt radiological countermeasures for astronauts. Thanks to the NASA Space Radiation Laboratory (NSRL) at Department of Energy's Brookhaven National Laboratory, it is now possible to simulate galactic cosmic radiation (GCR) that occurs in space and to determine the effects on biological models. We have initiated new experiments to determine if and how metformin might be a promising radioprotector from cosmic radiations. While effects of space radiation on the development of advanced cancer may not be an acute problem during an astronaut's time in space, this remains highly speculative and additional research is required to develop methods to reduce either short or long-term effects going forward. Thus, we initiated experiments with metformin, an approved drug that is used by millions of Americans for controlling type 2 diabetes.</p> <p>By way of background, metformin is a biguanide compound used in the treatment of type 2 diabetes mellitus, showing very low cytotoxic effects and that was FDA (Food & Drug Administration) approved in the 1990s. Metformin has been reported to decrease oxidative stress and DNA damage in vitro as well as in vivo, also decreasing chronic inflammation. Metformin acts mainly through the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK), which has pleiotropic effects downstream on cell metabolism. Furthermore, metformin is able to target mitochondria, inhibiting the complex I of the electron transport chain (ETC), but the mechanisms underlying this process have not been completely elucidated. Because of its antioxidant effects, we investigated the role of metformin as a radioprotective compound. One single dose of metformin (0.5-1 mM) on human colon epithelial cells (HCECs) and human skin fibroblasts (BJs), showed an increase in the expression of AMPK alpha subunit phosphorylation and superoxide dismutase 1 (SOD1), during the first 72 hours. Interestingly, SOD1 has a crucial role protecting against oxidative DNA damage and its overexpression is associated with radioresistance in human glioma cells. Furthermore, a decrease of the basal DNA damage (phosphorylation of H2AX at Ser 139 foci) and in reactive oxygen species (ROS) production was observed. Moreover, metformin treatment enhanced DNA damage responses (DDR) 24 hours after exposure of 2Gy of gamma-rays. To evaluate the radioprotective effect of metformin, cells were treated one time and irradiated 72 hours later, with 2, 4, and 6 Gy doses of gamma-rays. Cells were seeded at low density (200-1000 cells) and a colony formation assay was analyzed after 21 days. Metformin showed an increase in the surviving fraction of cells compared to the irradiated controls. Next, we investigated the radioprotective effect of metformin in vivo. Wild type 129/Sv mice were injected once per day with metformin 200 mg/kg, for three consecutive days prior exposure of 7.5 Gy of X-rays and sacrificed after 24 hours. Metformin pre-treatment was able to dramatically decrease DNA damage (p53 binding protein 1 foci) in mouse lung and colon tissues as well as the number of micronuclei in bone marrow cells, compared to the irradiated controls. Notably, when mice were irradiated at the dose of 10 Gy X-rays post-metformin treatment, an increase of 30% in the surviving fraction was observed over non protected mice. In summary, our preliminary data can be interpreted to suggest that metformin might act as a radioprotector from GCR, potentially lowering the risk of cancer initiation or promotion in astronauts.</p>
<p>Bibliography Type:</p>	<p>Description: (Last Updated: 02/21/2024)</p>
<p>Articles in Peer-reviewed Journals</p>	<p>Luitel K, Kim SB, Barron S, Richardson JA, Shay JW. "Lung cancer progression using fast switching multiple ion beam irradiation and countermeasure prevention." Life Sciences in Space Research. Life Sci Space Res (Amst). 2020 Feb;24:108-15.Epub 2019 Aug 1. https://doi.org/10.1016/j.lssr.2019.07.011 ; PubMed PMID: 31987474; PubMed Central PMCID: PMC6991460 [Note reported previously in Nov 2019 as "In press, corrected proof, available online August 1, 2019."], Feb-2020</p>