Fiscal Year:	FY 2018	**Task Last Updated:**	FY 11/11/2017
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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Comments:			
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No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
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Key Personnel Changes/Previous PI:			
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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 exposure associated tumor initiation and progression. Although biological mechanisms of normal tissue radiation injury are not completely understood, the roles of specific pathways in some cell types are becoming elucidated. While cell death is generally believed to be one the main causes of tissue injury from exposure to higher doses of low and high LET radiation, the dose and dose rates likely to be encountered by an astronaut on long-term missions into deep space are unlikely to cause massive cell death. Pathological manifestations after low-dose space radiation should be strongly influenced by non-cytotoxic radiation effects, resulting in incremental small changes in cell function, immune (micro-environmental) altered responses, and changes in metabolism. To more fully understand the tissue effects of exposure to space radiation compared to background cancer on Earth, it will require a more integrated "omics" and biological end point analysis as is proposed in this focused proposal using mouse models to help form the basis of a new description of radiation quality effects and cancer risk. Our published data (Clin Cancer Research, 2014) led us to the hypothesis that protracted/fractionated high LET irradiation can have long-term effects by changing the microenvironment in tissues leading to a pro-inflammatory cancer progressing phenotype. Importantly, the microarray signatures in these published studies on the K-ras lung cancer susceptible mouse model of lung cancer were shown to be applicable to overall survival in humans with lung and breast cancer. Thus, the studies proposed are likely to be applicable to human risks. In the current proposal we will test this hypothesis rigorously with normal mice, mice susceptible to lung cancer (LA1-Kras), and a colon cancer susceptible mouse model (CPC:APC) by incorporating the countermeasure arm in already approved studies. We have already established dose responses for tumor incidence in the K-ras and CPC;APC mouse. We will conduct experiments with these mouse models of cancer susceptibility and WT mice using a GCR (galactic cosmic ray) simulation that involve fast switching of three ion Si, He, and protons using low doses (total 30cGy) and dose rates (0.5 cGy/min). We will also test if an oral deliverable countermeasure, CDDO (with a known mechanism of action) using mission relevant irradiation doses can significantly decrease tumor incidence. As another approach we will compare CDDO to aspirin during the Fall 2017 NASA Space Radiation Laboratory (NSRL) run. We will focus on acute (24-48 hrs) as well as intermediate/persistent effects (14-100 days post-IR). A subset of mice will be maintained post-IR ~150-250 days to track tumor formation. We will conduct tissue micro-dissections and “omics” analyses of normal tissues, precancerous lesions, malignant lesions, and cleared margins surrounding the precancerous lesions in mice with and without being provided the medical radioprotector, CDDO, or aspirin. We propose that using a variety of radiation qualities and biological models, we will be able to dissect the important difference between space radiation and terrestrial radiation. This will lead to improved risk quantification and development of new systems biology risk modeling approaches that can be extrapolated to human cancer risks. Reference Delgado O, Batten KG, Richardson JA, Xie XJ, Gazdar AF, Kaisani AA, Girard L, Behrens C, Suraokar M, Fasciani G, Wright WE, Story MD, Wistuba II, Minna JD, Shay JW. Radiation-enhanced lung cancer progression in a transgenic mouse model of lung cancer is predictive of outcomes in human lung and breast cancer. Clin Cancer Res. 2014 Mar 15;20(6):1610-22.
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. 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.
	Task Objective/Description: 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 orally 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 the 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 0.5cGy/min and a total combined dose of between 27-30cGy to more closely mimic the space environment on a trip to Mars and back. Contributions to Fundamental Research: This project contributes to NASA's mission by the discovery of novel tissue biomarkers resulting from space radiation effects that are different from terrestrial radiation of equivalent doses. These biomarkers should contribute to our understanding of pathways underlying radiation-associated increases in invasive (more lethal) cancers. A better understanding of these pathways should enable the development of effective countermeasures. Contributions to Human Health: Successful completion of this project will contribute to the development of models that could predict increased risk of more lethal cancers and potentially to approaches that may mitigate the increased risk if they are higher than expected. If novel targets are discovered and shown to have biological targets that can protect tissues from radiation-induced side effects, there is likely to be interest among other academic groups and pharmaceutical companies to develop new drugs directed at those targets. Overall, this project takes an innovative approach to an important unmet medical need.

Task Progress:	Progress: In the LA-1 lung cancer susceptible mouse model we can make the following conclusions: • 50cGy simulated solar particle event (sSPE) decreases the lifespan of LA-1 animals and results in a significant increase incidence of carcinoma. • 30cGy single dose exposure to protons (0.5cGy/min) does not increase the number of initiating lesions in the LA-1 animals 100 days post IR but overall incidence of carcinoma and survival are ongoing. • A GCR simulation of 20cGy protons, 5cGy Helium, and 5cGy Silicon (using fast switching) results in an increase in the number of initiating lesions in the LA-1 animals 100 days post IR. Incidence of carcinomas and overall survival are ongoing. • LA-1 mice on a CDDO diet during solar particle irradiation simulations exhibit a decreased incidence in invasive carcinoma in comparison to mice on control diet. • There are no hematological or other tissue toxicities even when mice were kept on CDDO for long periods of time (>100days) In the colon cancer susceptible (CPC;APC) and (WT) mouse model experiments we can make the following conclusions: • SPE simulation (sSPE) increases colon cancer initiation and progression in CPC;APC mice; • sSPE induces prolonged DNA damage and an increase in p53 mutations; • sSPE enhances senescence associated inflammation that is persistent; • CDDO provided 3 days prior to radiation exposure protects mice from sSPE induced colon cancer initiation and progression; • 5cGy (300 MeV/n) of a single dose exposure to Silicon does not increase cancer initiation or overall survival but 10cGy Silicon results in a >2-fold cancer initiation and an overall decrease in lifespan. Based on these findings, our initial GCR simulations in WT, lung, and colon susceptible mice were conducted with 5cGy and now 2cGy of Silicon. We conducted GCR simulations consisting of protons, helium, and silicon using a dose rate of 0.5cGy/min. We used 20cGy of protons (120 MeV/n), 5cGy of helium (250 MeV/n) and 5cGy of silicon (300 MeV/n) in the initial series of experiments. Two GCR simulations were conducted to determine if the order of sequential beams influence biological outcomes. Preliminary results suggest order of ions may be important. 1) GCRsim1 = Protons, then Helium, then Silicon (total dose 30cGy); 2) GCRsim 2 = Silicon, then Protons, then Helium. (total dose 30cGy); 3) Protons alone (total dose 30cGy) We observed GCRsim1 result in an increase in initiating lesions but not GCRsim2. Based on our early results we have a working model to test the reason why order of sequential beam may have biological consequences. In addition, we have irradiated a cohort of mice with an even lower dose of 27cGy reducing Silicon from 5cGy to 2cGy. Overall these experiments are designed to test the hypothesis that GCR simulations even at very low doses and dose rates may increase carcinogenesis as tested in WT and cancer susceptible mice and that a biological countermeasure will reduce the incidence of development of more lethal cancers. If we observe an increase in tumor formation with GCR simulations, we will conduct RNA transcriptomics and DNA sequencing and a variety of other molecular studies to determine if cancer susceptible and wild type mice have molecular changes that may indicate an increased risk of cancer. These studies should identify potential targets for biological countermeasures.
Bibliography Type:	Description: (Last Updated: 02/21/2024)
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