Fiscal Year:	FY 2016	**Task Last Updated:**	FY 03/02/2016
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:			
Project Type:	Ground	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-RADIATION. Appendix D: Ground-Based Studies in Space Radiobiology
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Flight Program:			
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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 age-appropriate 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, inducible EGFR mutant mice susceptible to lung cancer 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 models using Si, O, protons, and solar particle event (SPE) simulations and propose to demonstrate that oral deliverable CDDO (with a known mechanism of action) using mission relevant irradiation doses can significantly decrease tumor incidence (EGFR mutant mice without induction of mutant EGFR are essentially WT mice) or progression/invasiveness (doxycycline induction of mutant EGFR either before or after irradiation). We will focus on intermediate/persistent effects (14-100 days post-IR) including some long-term effects (~150-200 days). 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. 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.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	New project for FY2016.
Bibliography Type:	Description: (Last Updated: 11/27/2024)