Fiscal Year:	FY 2024	**Task Last Updated:**	FY 03/25/2024
PI Name:	Fornace, Albert M.D.		
Project Title:	Radiation Carcinogenesis by GCRsim in Animal Models for High Priority Cancer Types (NSCOR)		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	http://www9.georgetown.edu/		
Project Type:	Ground	**Solicitation / Funding Source:**	Directed Research
Start Date:	05/25/2022	**End Date:**	05/24/2025
No. of Post Docs:	1	**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
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 05/24/2025 per NSSC information (Ed., 5/2/24). NOTE: End date changed to 05/24/2024 per S. Mack/JSC. Original end date was 05/24/2023 (Ed., 5/22/23).		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Shubhankar, Suman Ph.D. (Georgetown University) Shay, Jerry (University of Texas Southwestern Medical Center at Dallas) Brenner, David (Columbia University)		
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Task Description:	Considering the high spontaneous incidence of gastrointestinal (GI) and lung cancer, an even modest increase by space radiation exposure could have a significant effect on astronauts' health risk estimates during and after long-duration manned space flights. However, there is substantial uncertainty for GI and lung cancer risk estimation from space radiation due to the lack of in vivo human data. The overarching goal of the current proposal is to specifically investigate cellular and molecular hypothesis-driven mechanisms in relevant mouse models that will contribute to carcinogenic risk estimates of GI and lung cancer after exposure to space radiation beams prioritized by NASA's Human Research Program (HRP). Specifically, this proposal builds on the data generated from previous NSCOR studies and seeks to determine incidence, tumor frequency, and grade as well as identify molecular perturbations in the target cells associated with GI and lung tumorigenesis through monitoring of changes in the tumor number, histology, gene/protein expression, and metabolome of the proposed model system after exposure to space radiation type beams. Having found modest effects in earlier studies with protons and considering the importance of assessing the effects of mixed beams, we have chosen high priority Galactic Cosmic Radiation (GCR) type beams for comparison with low-LET (gamma-rays) radiation in our proposed studies. The full-spectrum (33-ion) acute (single dose) and protracted (up to 6 weeks) GCRsim beams closely mimic the mixed particle radiation environment in deep space. Our overall hypothesis is that GCRsim exposure is more carcinogenic due to important qualitative differences from low-LET gamma rays. The overall objective of this proposal is to acquire quantitative and qualitative cancer data after full-spectrum GCRsim exposure to model the relative risk of GI and lung tumorigenesis and compare it to gamma radiation where human epidemiologic data are available. Our proposed Aims are: Aim 1. Quantitatively assess GI tumorigenesis in mouse models of GI cancer and collect samples for qualitative analysis. Aim 2. Understanding molecular signaling associated with space radiation-induced GI-tumorigenesis and functional alterations. Aim 3. Quantitatively and qualitatively compare effects of GCR-type irradiations on lung cancer initiation and progression in normal as well as lung cancer susceptible mice. Aim 4. Development of mathematical modeling for GI and lung cancer risk assessment.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	According to estimations from the American Cancer Society (ACS), the lifetime risk of developing colorectal (1 in 23 for men and 1 in 25 for women) and lung (1 in 16 for men and 1 in 17 for women) cancer is significantly high in the US population. Considering the high prevalence of GI and lung cancer, an even slight increase in the incidence of GI and lung cancer in astronauts due to space radiation exposure is a critical health concern and has a significant impact on the planning of upcoming manned deep space exploration missions. In addition to cancer risk estimation studies after space radiation exposure, investigations on the persistence of oxidative and inflammatory stress after space radiation and its role in GI and lung cancer development may provide insight into mutagenic processes affecting genome integrity and carcinogenesis. The significance and deliverable of this project are to improve the estimates of GI and lung cancer risk after simulated galactic cosmic radiation (GCR) exposure and to identify plausible targets for the development of medical countermeasures (MCM).
Task Progress:	Pointwise progress made for Aim/Projects 1–4 is summarized below. (1) Dose-response investigations were conducted to generate quantitative data on GI tumorigenesis following acute exposure to GCRsim (10-75 cGy) in both male and female Apc1638N/+ mice. The results revealed a significant increase in GI-tumorigenesis across all GCRsim doses tested compared to the control group. (2) To assess the impact of GCRsim dose rate on GI-tumorigenesis, we conducted exposures at levels of 25, 50, and 75 cGy in both acute and chronic settings. For the chronic simulation of GCRsim exposure, mice received fractionated doses (2.08 cGy/day) over specific durations: 25 cGy (administered 6 days per week for two weeks), 50 cGy (6 days per week for four weeks), and 75 cGy (6 days per week for six weeks). Both acute and chronic exposures led to significantly elevated levels of GI tumorigenesis in male and female mice compared to the control group. These findings indicate that the occurrence of GI tumorigenesis following GCR exposure appears to be unaffected by the dose rate. (3) GI tumor data resulting from equivalent doses of p+He (45.7 cGy), HZE (4.37 cGy), and GCRsim (50 cGy) were compared to discern the contributions of heavy ions to GI-tumorigenesis. Comparing intestinal tumor data from GCRsim with equivalent doses of heavy ions revealed a correlation between heightened GI-tumorigenesis and doses from the heavy-ion (HZE) fraction. This is evidenced by the significantly greater tumor induction per unit dose (cGy) observed for HZE compared to p+He and GCRsim exposures. (4) Male Apc1638N/+ mice were exposed to 50 cGy of 4-ion GCRsim (60% H, 20% He, 5% O, and 5% Si), and gastric tumors were counted at 5 months post-exposure. Both 4-ion GCRsim and gamma-ray exposure caused an increase in gastric tumor (adenoma) and carcinoma development relative to the sham group. Our findings suggest that exposure to GCRsim is more likely to cause gastric cancer than low-LET radiation. (5) Analysis of intestinal tissues and serum collected five months post-irradiation revealed a significant increase in the levels of LINE1 element-specific amplicons in serum DNA from the irradiated group compared to the control. Furthermore, there was a decrease in DNase2 and TREX1 mRNA levels in intestinal epithelial cells following irradiation, albeit with no significant change in DNase1 levels. We also observed a marked decrease in TREX1 immunostaining and protein levels in irradiated mouse intestinal tissues compared to controls. These findings underscore the impact of GCRsim exposure on the expression of key nucleases involved in DNA degradation and the maintenance of extracellular DNA levels in the mouse intestine. (6) Exposure to acute GCRsim leads to activation of the cGAS-STING signaling pathway in the mouse intestine. Moreover, downstream signaling molecules of the cGAS-STING pathway, including phospho-TBK1 and phospho-IKKa, were also altered after radiation exposure. Notably, these alterations were more pronounced in GCRsim-exposed tissues compared to those exposed to gamma radiation. (7) Prolonged crewed space flight poses health risks due to exposure to galactic cosmic radiation, with previous research at the NASA Space Radiation Laboratory indicating that HZE ion components of GCR lead to persistent inflammation, increased mutations, and elevated cancer rates. Utilizing the 33-beam galactic cosmic radiation simulations (GCRsim) at NSRL, experiments on a lung cancer susceptible mouse model, i.e., K-rasLA-1 mice showed increased lung adenocarcinoma incidence with higher doses and prolonged exposures, particularly when neutron exposure was added. 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 exposure on the Martian surface. Overall, carcinogenesis risks are enhanced with doses expected on a round trip to Mars. We also observed that risks were reduced

when the NASA official 33-beam GCR simulations are provided at high dose rates compared to low dose rates.

(8) Administration of metformin (0.5 mM) showed radioprotective effects in vitro on BJ human fibroblasts, increasing DNA damage repair, and increasing SOD1 expression in the nucleus. Importantly, metformin (200 mg/kg) pre-administration for only 3 days in wild type 129/sv mice, decreases the formation of micronuclei in bone marrow cells and DNA damage in colon and lung tissues compared to control irradiated mice at sub-lethal and lethal doses, increasing the overall survival fraction by 37% after 10 Gy total body irradiation. We next pre-treated with metformin and then exposed 129/sv mice to the 33-beam GCRsim. We found metformin pre-treatment decreases the presence of bone marrow micronuclei and DNA damage in colon and lung tissues and an increase of 8-oxoguanine DNA glycosylase-1 (OGG1) expression. We demonstrate a radioprotective effect of metformin through an indirect modulation of gene expression involved in cellular detoxification rather than its effects on mitochondria.

(9) We developed and implemented a mechanistically-motivated mathematical carcinogenesis model that includes both TE and NTE components, and applied it to the data on intestinal tumorigenesis in Apc1638N/+ tumor-prone mice. Importantly, when mixtures of several space radiation types, such as protons and different species of heavy ions, bombard the same biological target, it is not a trivial task to quantify the contribution of each radiation type and predict the overall effect of the mixture. This is the case because, when dose response shapes for the mixture components are not linear (e.g., due to NTE contributions), simply adding the predicted cancer risk contributions of each radiation type together will not correctly predict the risk from the entire mixture. In other words, the seemingly intuitive simple effect additivity (SEA) approach is known to be incorrect for curved dose responses, and more specialized alternative synergy theories such as incremental effect additivity (IEA) are required.

(10) We employed the incremental effect additivity (IEA) methodology to predict the tumorigenic effectiveness of mixtures of space radiation types, based on the fits of our model to data for individual radiation types: protons (1000 MeV/n; 50 to 120 cGy; 0.22 keV/µm, 40 mice), 4He (250 MeV/n; 5 to 50 cGy; 1.6 keV/µm, 92 mice), 12C (290 MeV/n; 10 to 200 cGy; 13 keV/µm, 60 mice), 16O (325 MeV/n; 5 to 50 cGy; 22 keV/µm, 66 mice), 28Si (300 MeV/n; 5 to 140 cGy; 69 keV/µm, 136 mice), 56Fe (1000 MeV/n; 5 to 160 cGy; 148 keV/µm, 90 mice), gamma rays (5-200 cGy, 127 mice). At the current stage of the project, a new data set on tumorigenesis after 33-ion GCRsim mixture exposures (25, 50 and 75 cGy; acute and chronic) is being assembled. This type of mixture is more detailed and more realistic of the space exposure environment. We are working on implementing our TE+NTE model formalism and the IEA synergy theory approach on this data set to provide a more accurate assessment and mechanistic explanation for the overall mixture effect, and for the contributions of its individual components.

Bibliography Type:	Description: (Last Updated: 05/01/2024)
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