Fiscal Year:	FY 2022	**Task Last Updated:**	FY 10/28/2021
PI Name:	Fornace, Albert M.D.		
Project Title:	Space Radiation-Induced Persistent Estrogenic Response and Risk of Breast Cancer Development		
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:	(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:	http://www9.georgetown.edu/		
Project Type:	Ground	**Solicitation / Funding Source:**	2018 HERO 80JSC018N0001-Crew Health and Performance (FLAGSHIP, OMNIBUS). Appendix A-Flagship, Appendix B-Omnibus
Start Date:	01/02/2020	**End Date:**	01/01/2024
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	Ed. note (December 2020): Original Principal Investigator was Kamal Datta, M.D., who is now affiliated with NIH, as of early 2019. PI changed to Albert Fornace, M.D., before grant was awarded.		
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Task Description:	Based on epidemiological analysis of radiation-exposed human cohorts, it is projected that space radiation could significantly increase breast cancer incidence and mortality among female astronauts. However, there is large uncertainty in breast cancer risk estimation due to a lack of in vivo data. The proposed study aims to acquire in vivo quantitative and qualitative data on space radiation-induced breast cancer risk using a mouse model approach. Further, we also aim to test “persistent estrogenic response” (PER) signaling as a target to develop a potential countermeasure against space radiation-induced mammary tumorigenesis. We further hypothesize that targeting galactic cosmic radiation (GCR)-induced PER using an FDA (Food & Drug Administration) approved selective estrogen receptor modulator (SERM) will decrease the risk of mammary tumorigenesis. We plan to test our hypothesis by pursuing the following Specific Aims: Aim 1. Quantitatively compare effects of simulated GCR dose rates on mammary tumor incidence and grade in the ApcMin/+ (Adenomatous polyposis coli Multiple intestinal neoplasia/+) tumor model. Aim 2. Characterize GCR dose-rate effects on PER in relation to mammary tumorigenesis. Aim 3. Determine roles of SERM in countering space radiation-induced PER and mammary tumorigenesis. Aim 4. Risk assessment (modeling) of mammary tumorigenesis after space radiation exposure. Key deliverables for this project are: 1) Develop a mathematical model for GCR dose rate-based breast cancer risk estimation, 2) Identify early markers of GCR-induced mammary tumorigenesis, and 3) Test potential mechanism-based FDA-approved countermeasure agents.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Based on 2015–2017 data, approximately 12.9 percent of women in the United States are projected to be diagnosed with breast cancer at some point during their lifetime. The annual rate of new cases and mortality from breast cancer in the United States is 128.5 per 100,000 and 20.1 per 100,000 women, respectively. Considering the high frequency of breast cancer in the American population, and even a small increase by space radiation could have a major impact on risk estimates and planning of future space missions. In addition to risk estimation, studies on persistent estrogenic response after space radiation and its role in driving mammary tumorigenesis may provide insight into signaling events affecting carcinogenesis. The significance and deliverables of this project are to improve the estimates of breast cancer risk in women astronauts and to identify and test plausible targets for the development of mitigation strategies.
Task Progress:	The risk of space radiation-induced breast cancer in female astronauts is expected to increase during and after undertaking prolonged space missions such as missions to Mars. However, studies comparing the effects of low and high dose rate space radiation exposures are few and no studies are available in the literature comparing mammary tumorigenesis after low and high dose rate galactic cosmic radiation (GCR) exposures. Previous studies using mathematical and statistical model systems have demonstrated a significant probability of developing cancer after a Mars mission secondary to chronic radiation exposure. Despite these findings, large uncertainties still exist when making risk projections mainly because there are limited epidemiological and biological data to describe the effects of GCR in human tissues. One general approach for risk assessment is to determine the relative biological effectiveness (RBE) of various parameters for space radiation compared to terrestrial radiation exposures. Since there is sufficient statistical sampling for the latter, risk estimates can then be “extrapolated” to space radiation using the RBE scaling factor (typically relative to gamma rays); needless to say, the reliability of the models for RBE determination is key. While the application of scaling factors is generally accepted to be the only practical approach to human cancer risk estimation for space radiation, a central, testable hypothesis is that qualitative and quantitative differences between space radiation and gamma-ray effects are maintained across species, such as from mouse to man. Understanding how to scale such risks in model systems will provide the best possible framework for undertaking the same scaling of cancer risks in humans. To use this approach requires the collection of relevant quantitative and qualitative data for oncogenic and pre-oncogenic endpoints in animal model systems relevant to human mammary cancer, as well as a sufficient understanding of the comparative molecular mechanisms involved in tumorigenesis. We proposed to use female ApcMin/+ mice to acquire the quantitative and qualitative biological data using a range of radiation doses and dose rates simulating GCR to develop a reliable risk prediction model that includes ‘both direct and non-targeted effects’. Additionally, dissecting mechanisms of space radiation-induced persistent estrogenic response (PER) will allow “evaluation of early markers for relevance as surrogates for late disease outcomes”. Overall, the proposed research will increase our understanding of breast cancer risk from space radiation and enhance NASA’s breast cancer risk prediction as well as countermeasure capabilities. Accomplishments (Jan-Dec 2021): 1. During the Spring-2021 beam run, a total of 220 mice (ApcMin/+ and wild-type female) were exposed to acute (25 and 75 cGy) and chronic (25 and 75 cGy) of full-GCRsim (33-beam). Additional ApcMin/+ and wild-type female mice were exposed to gamma radiation. After 100 to 120 days post-irradiation, we have harvested samples for persistent estrogenic response (PER) and breast tumorigenesis studies. We have collected serum, normal mammary gland, mammary tumors, and ovaries at the time of sacrifice, and detailed analysis of pre-neoplastic markers and mammary tumorigenesis is ongoing. 2. In order to acquire baseline tumorigenesis data after gamma-rays (using 137Cs source) exposure for relative biological effectiveness (RBE) calculations, we exposed female ApcMin/+ to 10 to 100 cGy range of gamma-rays, and relevant tissue samples (mammary gland, ovaries, and serum) from these mice have been harvested. 3. We also obtained initial tumorigenesis data using female ApcMin/+ mice at 25 to 75 cGy dose range for both acute and chronic full-spectrum GCRsim. Initial tumorigenesis data using >20 mice/group indicates a good signal-to-noise for mammary tumorigenesis in ApcMin/+ mice, and additional NASA Space Radiation Laboratory (NSRL) beam time has been proposed for exposures to reach >50 mice/group (as estimated in power analysis). 4. While statistically robust mammary tumorigenesis quantitative and qualitative data is unlikely to be available until 2023, we analyzed known histological and molecular markers of mammary preneoplastic lesions in normal-appearing mammary gland samples obtained from sham, and 50 cGy of gamma-rays or simulated GCR (33 beams) exposed ApcMin/+ mice. A set of histological parameters (ductal overgrowth, alveologenesis, and alveolar hyperplasia) and molecular markers with an established role in both mouse and human breast tumorigenesis were analyzed. 5. The 33-beam GCR exposure led to increased cell proliferation and ductal outgrowth in normal breast tissue that indicates a higher cancer risk, relative to gamma-rays. The mRNA expression analysis from gamma- and GCR-exposed mice breast tissue showed a significantly higher expression of Depdc1, Nusap1, Spp1, and Rrm2 genes, relative to sham controls. Further, Spp1 and Rrm2 expression was significantly higher in the GCR group, relative to gamma-rays, whereas Depdc1 and Nusap1 were significantly overexpressed in both gamma and GCR groups. Radiation quality-dependent increases in Spp1 and Rrm2 protein expression were also noted in IHC stained sections.

	6. Initial optimization studies for non-invasive magnetic resonance imaging and MR spectroscopy (MRI/MRS) using control and gamma-exposed female ApcMin/+ and WT mice are ongoing. Once MRI/MRS optimization is completed, we will use GCR-exposed female ApcMin/+ and WT mice to study mammary tumor progression and in situ metabolic alterations. 7. We have applied for beam time during the Spring (acute GCR) and Summer (chronic GCR) beam run in 2022 (approval pending). Additional studies with gamma radiation have been initiated and samples are being processed. Results will be compared to the high dose rate (acute) GCR exposures, and acute gamma radiation exposure will be used as a baseline reference. After 100 to 120 days post-irradiation we will collect serum, urine, and mammary gland/tumor samples at the time of sacrifice. Mammary tumors will be carefully counted and tumor size will be measured. Tumors will be analyzed histologically to document differences in tumor grade between gamma and space radiation dose rates.
Bibliography Type:	Description: (Last Updated: 05/15/2025)
Abstracts for Journals and Proceedings	Suman S, Datta K, Shuryak I, Brenner D, Fornace AJ Jr. "Persistent estrogen signaling in space radiation-induced breast cancer development." 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021
Abstracts for Journals and Proceedings	Fornace AJ Jr, Suman S, Shay J, Meltzer P, Brenner D. "Space radiation-induced tumorigenesis, risk modeling, long-term injury responses, and mitigation strategy: NSCOR project update." 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021
Abstracts for Journals and Proceedings	Kumar K, Moon BH, Angdisen J, Datta K, Fornace AJ Jr, Suman S. "Breast cancer risk assessment using markers of preneoplastic lesions in space radiation-exposed female ApcMin/+ mice." 67th Annual Meeting of the Radiation Research Society, Virtual, October 3-6, 2021. Abstracts. 67th Annual Meeting of the Radiation Research Society, Virtual, October 3-6, 2021. , Oct-2021
Abstracts for Journals and Proceedings	Fornace AJ Jr. "Carcinogenesis by space radiation: How much more dangerous is it than gamma rays, and what mechanisms contribute to tumorigenesis?" 67th Annual Meeting of the Radiation Research Society, Virtual, October 3-6, 2021. Abstracts. 67th Annual Meeting of the Radiation Research Society, Virtual, October 3-6, 2021. , Oct-2021