Fiscal Year:	FY 2023	**Task Last Updated:**	FY 10/28/2022
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		
PI Email:	af294@georgetown.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	202 687-7843
Organization Name:	Georgetown University		
PI Address 1:	Dept. of Oncology, Lombardi Comprehensive Cancer Center		
PI Address 2:	Research Building, Room E504, 3970 Reservoir Rd., NW		
PI Web Page:			
City:	Washington	**State:**	DC
Zip Code:	20007-2126	**Congressional District:**	1
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
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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
Contact Monitor:	Elgart, Robin	**Contact Phone:**	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
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.		
COI Name (Institution):	Brenner, David Ph.D. (Columbia University) Johnson, Michael Ph.D. (Georgetown University) Li, Xin Ph.D. (Georgetown University) Suman, Shubhankar Ph.D. (Georgetown University)		
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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 a 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 GCR-induced PER using an FDA-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/+ 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:	Breast cancer is the second most common cancer among women in the US. According to current breast cancer incidence data, approximately 12.9 percent of women in the United States will be diagnosed with breast cancer at some point in their lives. 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, 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 the mechanisms of space radiation-induced persistent estrogenic response (PER) will allow the 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. Task Book accomplishments (Jan-Dec 2022): 1. We participated in the spring and summer 2022 NASA Space Radiation Laboratory (NSRL) runs. We exposed female ApcMin/+ and C57BL6 wild-type (WT) mice to acute and chronic full-spectrum GCRsim (33-ion cocktail) beams (dose range of 25 to 75 cGy). 2. We initiated a pilot study to test metformin (0.1% through diet) as a potential countermeasure against space radiation-induced mammary tumorigenesis in ApcMin/+, and results are awaited by early 2023. 3. 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 a 10 to 100 cGy range of gamma-rays, and relevant tissue samples (mammary gland, ovaries, and serum) from these mice have been harvested. After 100 to 110 days post-irradiation, we harvested samples for breast tumorigenesis studies. We have collected serum, normal mammary gland, mammary tumors, and ovaries at the time of euthanasia and performed a detailed analysis of pre-neoplastic markers, and mammary tumorigenesis is ongoing. So far, our tumorigenesis data indicate a good signal-to-noise in ApcMin/+ mice for mammary tumorigenesis and provide a clear dose response. Both acute and chronic GCRsim-exposed mice displayed higher mammary tumor incidence relative to gamma-ray and control groups. Finally, tumorigenesis data from low-dose-rate (chronic) GCRsim will be compared to the high-dose-rate (acute) GCRsim exposures, and acute gamma radiation will be used as a baseline reference to estimate relative biological effectiveness (RBE). 4. To study chronic GCR-induced persistent estrogenic response (PER), serum and mammary tissue samples from control and chronic 33-ion GCRsim (50 cGy) exposed ApcMin/+ were harvested. We also correlated tumorigenic changes with PER-signaling at both mammary tissue and systemic levels. 5. While statistically robust mammary tumorigenesis quantitative and qualitative data are 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 and hyperplasia) and molecular markers with an established role in both mouse and human breast tumorigenesis were analyzed. The 33-beam GCR exposure led to increased cell proliferation and ductal outgrowth in normal mammary tissue, which indicates a higher cancer risk

	relative to gamma rays. The mRNA expression analysis from gamma- and GCR-exposed mouse mammary tissue showed a significantly higher expression of Spp1 mRNA relative to the control group. Radiation quality-dependent increases in SPP1 protein expression were also noted in IHC-stained sections. 6. We also analyzed chronic GCRsim-induced changes in estrogen signaling mediators, i.e., serum estrogen levels and its receptor, estrogen receptor alpha (ERa) and estrogen-related receptor-alpha (ERRa), expression in mammary tissue. Chronic GCRsim-exposure resulted in increased serum estradiol levels that also coincided with significantly higher expression of ERa and ERRa mRNA. In concurrence with increased mRNA expression, the protein expression of ERa and ERRa were also higher in GCRsim-exposed ApcMin/+ mice, relative to the control group. Further, both ERa and ERRa downstream targets with their known function in mammary ductal cell proliferation and tumorigenesis were also upregulated. Altogether, we found PER-induced activation of both ERa and ERRasignaling that has implications for higher mammary tumorigenesis after GCRsim exposure. 7. Increased ductal epithelial cells cell proliferation marked by higher expression of CyclinD1 (a cell proliferation marker downstream of ERa) and increased expression of SPP1 (a mammary preneoplasia marker, downstream of ERRa) was noted in chronic GCRsim exposed ApcMin/+ mice relative to unirradiated controls. Further, increased serum levels of SPP1 were also noted in GCR- exposed mice. Altogether, GCR-induced PER coincided with the activation of the ERa/ERRasignaling axis and its downstream targets. 8. Initial optimization studies for non-invasive magnetic resonance imaging (MRI) have been completed in female Apcmin/+, and mouse mammary gland magnetic resonance spectroscopy (MRS) has been optimized using female WT mice.
Bibliography Type:	Description: (Last Updated: 04/18/2024)
Abstracts for Journals and Proceedings	Suman S, Kumar K, Moon B, Angdisen J, Datta K, Fornace Jr AJ. "Analysis of preneoplastic breast cancer risk markers after simulated galactic cosmic radiation (GCR) in Apcmin/+ mice [#1133-000311]." NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. Abstracts. NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022
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Articles in Peer-reviewed Journals	Kumar K, Moon BH, Datta K, Fornace AJ Jr, Suman S. "Simulated galactic cosmic radiation (GCR)-induced expression of Spp1 coincide with mammary ductal cell proliferation and preneoplastic changes in ApcMin/+ mouse." Life Sci Space Res (Amst). 2023 Feb;36:116-22. https://doi.org/10.1016/j.lssr.2022.09.006 ; PubMed PMID: 36682820 , Feb-2023