Fiscal Year:	FY 2021	**Task Last Updated:**	FY 01/28/2021
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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
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No. of Post Docs:	0	**No. of PhD Degrees:**	0
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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 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:	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 women 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 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 galactic cosmic rays (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 γ 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 γ -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. Taskbook accomplishments: The Covid-19 shutdown has had a major impact on our productivity on the first year (Jan-2020 to Dec-2020) of this project. Georgetown University had to shut down after 16th March due to DC Government guidelines. Due to restrictions on researchers and technician access to the laboratory and animal facilities, many mice had to be sacrificed. After the initial phase of complete shutdown, our researchers and technicians were granted special access to perform essential lab duties, such as maintenance of mice colony while non-essential benchwork was not allowed, and new animal orders were also canceled that impacted (delayed) planned progress on the ongoing studies. We have our plan in place to maximize our research efforts with a shift system, which is expected to reach ~50-75% of the required productivity. Despite Covid-19 related delays and reduced occupancy in the lab, we continued our studies with maximum possible efficacy and made satisfactory progress in the latter part of the year. We are expecting to have enough samples available to continue molecular studies at beginning of 2021. Pointwise summary of accomplishments during Jan-Dec 2020 is as follows: 1. While Spring-2020 beam run was canceled and expected experimental progress was delayed, we successfully participated during Summer-2020 to access full-spectrum chronic and acute GCRsim beams at NASA Space Radiation Laboratory (NSRL) and exposed female ApcMin/+ and wild-type (WT) mice to 50 cGy dose of acute and chronic full-spectrum GCRsim (33-ion cocktail) beam during the summer (NSRL20B) beam run. After 100 to 120-day post-irradiation we collected serum, urine, mammary gland/tumor, and ovaries at the time of sacrifice and detailed analysis of pre-neoplastic markers, mammary tumorigenesis, tumor size, tumor grade, as well as histological immunophenotyping is ongoing. 2. We also obtained initial tumorigenesis data using female ApcMin/+ mice after 50 cGy of chronic full-spectrum GCR-sim radiation. Our initial tumorigenesis data using >20 mice in control and chronic full-spectrum GCR-sim group indicates a good signal-to-noise in ApcMin/+ mice, and future studies with a lower (25 cGy) and a higher (75 cGy) dose are likely to provide a clear dose-response. 3. In order to acquire baseline tumorigenesis data after γ-rays (using 137Cs source) exposure for relative biological effectiveness (RBE) calculations, we exposed female ApcMin/+ to 10, 50, and 100 cGy γ-rays and all the relevant tissue samples (mammary gland, ovaries, and serum) from these mice will be harvested at 120 days post-exposure (March-2021).

	4. Extending our earlier finding of increased estrogen receptor a (ERa) expression after proton exposure, we also studied ERa downstream FoxP3 expression using immunohistochemistry. Female ApcMin/+ mice were exposed to 1 GeV protons (1.88) and 137Cs γ-rays (2 Gy). Mice were sacrificed 100 to 110 days after irradiation, and mammary tumors and tumor grades were assessed. Protons induced more adenocarcinomas relative to γ-rays, and proton-induced tumors show greater ERa positivity and higher activation of the ERa downstream FoxP3 (a forkhead box transcription factor) relative to γ-rays. FoxP3 is known to play an important role in the development and function of immune regulatory T cells (Tregs). Effective evasion of the immune system by tumor cells is required during tumor progression and metastasis and increased activity of Tregs via activation of FoxP3 represents a critical mechanism of immune evasion by tumors. Further studies will focus on immunophenotyping of space radiation-induced mammary tumors and will seek to understand the involved mechanisms of tumor progression. 5. Assessment of serum estradiol in ApcMin/+ mice indicated a persistent increase in serum estrogen levels after proton radiation relative to γ-rays and this also correlated well with ductal hyperplasia (a marker of a pre-neoplastic lesion) marked by increased Ki67 (proliferation marker) after exposure to proton radiation relative to γ-rays. 6. Exposure to proton radiation led to increased mammary tumor frequency at both proton radiation doses compared with γ-rays. The calculated relative biological effectiveness (RBE) for proton radiation-induced mammary tumorigenesis was 3.11 for all tumors and >5 for malignant tumors relative to γ-rays. Tumor frequency per unit of radiation was higher at the lower dose, suggesting a saturation effect at the higher dose. As the grant progresses and additional in vivo quantitative data using GCR types beams are becoming available to further refine these RBE values, and risk estimation will be applied. 7. We applied and received approved beam time to conduct our experiments during Spring-2021 beam run using acute and chronic 25 and 75 cGy of full-GCRsim. Additional studies with γ radiation have been initiated at Georgetown University (GU) and samples are being processed. Results will be compared to the high-dose-rate (acute) GCR exposures, and acute γ 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 γ and space radiation dose rates.
Bibliography Type:	Description: (Last Updated: 05/15/2025)
Abstracts for Journals and Proceedings	Brenner DJ, Shuryak I, Fornace AJ Jr., Suman S, Datta K, Slaba TC, Blattnig SR, Norman RB, Plante I. "Mechanistically-based model development for space radiation risk assessment estimating the radiation quality dependencies for GCR-induced targeted vs. non-targeted health effects." 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. Meeting abstract. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020
Abstracts for Journals and Proceedings	Suman S, Datta K, Shuryak I, Brenner DJ, 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. Meeting abstract. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Suman S, Shuryak I, Kallakury B, Brenner DJ, Fornace AJ Jr, Johnson MD, Datta K. "Protons show greater relative biological effectiveness for mammary tumorigenesis with higher ERa and HER2 positive tumors relative to γ-rays in APCMin/+ mice." Int J Radiat Oncol Biol Phys. 2020 May 1;107(1):202-11. Epub 2020 Feb 6. https://doi.org/10.1016/j.ijrobp.2020.01.031 ; PubMed PMID: 32036005 , May-2020