Fiscal Year:	FY 2024	**Task Last Updated:**	FY 10/30/2023
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): The original Principal Investigator (PI) 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. In January 2023, the Co-Investigator (Dr. Michael Johnson) was replaced with Dr. Marc E. Lippman, who is a world-renowned breast cancer expert and Professor of Oncology at the Lombardi Comprehensive Cancer Center at 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 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 (January to December 2023):_[1] We participated in the NASA Space Radiation Laboratory (NSRL) spring/summer 2023 beam run and expanded our studies to obtain a statistically robust mammary tumorigenesis dataset with an adequate number of mice. We exposed a total of 190 mice (125 female ApcMin/+ and 65 female C57BL6) to acute GCRsim radiation at doses ranging from 25 to 75 cGy. In parallel with GCR exposure, we also exposed 30 ApcMin/+ mice to 75 cGy of gamma-rays at Brookhaven National Laboratory (BNL). At 100 to 120 days post-exposure, we sacrificed the female ApcMin/+ mice (125 mice) and collected mammary tissue samples. We have also harvested serum and tissue samples, including mammary gland and ovaries, for detailed analyses of pre-neoplastic markers, mammary tumorigenesis, tumor size, tumor grade, and histological immunophenotyping. Additionally, wild-type C57BL6J females, both those with intact ovarian function at the age of 22 to 26 weeks and those with ceased ovarian function at the age of 52 to 62 weeks, were exposed to acute GCR radiation. At the 120-day post-exposure time-point, we have harvested serum and tissue samples from their mammary glands and ovaries. We are currently conducting detailed analyses of estrogen biosynthetic pathway genes/enzymes in the ovaries and adipose tissues, which serve as an extraovarian source of estrogen, particularly in aged mice with ceased ovarian estrogen production._[2] The mammary tumorigenesis data compiled so far indicates a good signal-to-noise ratio in ApcMin/+ mice for mammary tumorigenesis and provides a clear dose-response for gamma, acute GCR, and chronic GCR beams in the 25 to 75 cGy dose range. Both acute and chronic GCRsim exposure in mice resulted in a higher rate of mammary tumor development compared to the gamma-exposed groups, and tumorigenesis was approximately equivalent after acute or chronic GCRsim._[3] In addition to tumorigenesis analysis and assessment of estrogen signaling in the mammary gland, we conducted a quantitative proteomics analysis of serum samples from control and acute GCR-exposed ApcMin/+ mice to understand the cross-talk between local and systemic factors after space radiation exposure. In total, we identified 1374 serum proteins, with a quantitative ratio over 1.2 considered as up-regulation, and a quantitative ratio less than 1/1.2 considered as down-regulation. We found that a total of 194 proteins were significantly upregulated, and 461 were downregulated. Cluster analysis of differentially expressed proteins (DEPs) and the principal component analysis

(PCA) plot clearly indicated a separation of irradiated and control groups.

[4] We used the Encyclopedia of Genes and Genomes (KEGG) database to identify enriched pathways of differentially expressed proteins (DEPs). The pathways with a corrected p-value < 0.05 were considered significant. We noted a significant number of proteins with established role in breast cancer development were upregulated in GCR-exposed mice.

[5] Obesity and increased adipogenesis are known risk factors for breast cancer development in women. To analyze space radiation-induced changes in abdominal fat, we employed a non-invasive MR-imaging and MR-spectroscopy and we noted that the percent of abdominal fat accumulation was significantly increased after 75 cGy GCR exposure, relative to the control group. Furthermore, we normalized the visceral fat area with the body weight of the mouse and observed that abdominal fat was increased in all the irradiated mice compared to the control group. Overall, this suggests that GCR exposure could result in increased fat accumulation in female mice, which is a well-established risk factor for mammary cancer development.

Bibliography Type:	Description: (Last Updated: 04/18/2024)
Abstracts for Journals and Proceedings	Kumar K, Angdisen J, Datta K, Fornace AJ, Suman S. "Simulated space radiation exposure activates ERalpha/ERRalpha/SPP1 signaling and induces mammary tumorigenesis in female ApcMin/+ mice." 17th International Congress for Radiation Research, August 27-30, 2023, Montreal, Quebec, Canada. Abstracts. 17th International Congress for Radiation Research, August 27-30, 2023, Montreal, Quebec, Canada. , Aug-2023
Papers from Meeting Proceedings	Kumar K, Angdisen J, Datta K, Fornace AJ, Suman S. "Activation of ERa/ERRa signaling coincides with overexpression of secreted phosphoprotein 1 during mammary tumorigenesis after GCRsim exposure." 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. Abstracts. 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. , Feb-2023