Fiscal Year:	FY 2020	**Task Last Updated:**	FY 06/30/2020
PI Name:	Story, Michael D Ph.D.		
Project Title:	Determining Gender Differences in the Incidence of Lung Adenocarcinoma After Space Radiation Exposure		
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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Zip Code:	75235-7320	**Congressional District:**	30
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2016-2017 HERO NNJ16ZSA001N-SRHHC. Appendix E: Space Radiobiology and Human Health Countermeasures Topics
Start Date:	09/01/2018	**End Date:**	08/31/2022
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No. of PhD Candidates:	1	**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:**	
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Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Lianghao, Ding Ph.D. (University of Texas Southwestern Medical Center, Dallas)		
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Task Description:	Uncertainties in radiation induced lung cancer risk estimation and its associated mortality rates are among the primary factors limiting the number of safe days an astronaut can spend in space. Initial lung cancer risks are based off epidemiological-based modeling and include cohorts such as the atomic bomb survivor life span study (LSS) whose estimates contain large confidence intervals and whose populations may not reflect astronauts on deep space missions. In order to calculate the permissible exposure limit (PEL) for astronauts it is necessary to collect further information on the risk of lung carcinogenesis due to radiation quality differences (relative biological effectiveness--RBE), sex disparities, and how effective biological countermeasures may reduce or mitigate these risks. The goal of this project is to provide sufficient data to bolster risk estimates and RBE values for lung carcinogenesis from the individual small, intermediate, and heavy charged particles that comprise galactic cosmic rays (GCRs) with doses comparable to what an astronaut may receive on a Mars mission. Additionally we will delineate any sex differences in radiogenic lung cancer risk resulting from space radiation exposure, provide sufficient evidence to validate GC4419, a Food & Drug Administration (FDA investigational new drug (IND), as an effective pharmaceutical countermeasure, and mechanistically define the biological processes associated with space radiation induced lung carcinogenesis.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	There are two areas where this research may benefit life on Earth. 1) Differences in both the incidence of and mortality arising from lung cancer between men and women have long been appreciated, with women generally having higher incidences and mortality rates than men. Epidemiological studies comparing pre- and post-menopausal women treated with hormone replacement therapy (HRT) have demonstrated that female sex hormones both elevated the incidence and aggressiveness at the time of presentation. These effects likely enhance the efficacy of other carcinogens such as radiation or tobacco smoke. We are following the production of estrogen for 8 weeks post-IR (irradiation) to determine whether space radiation is more effective at reducing estrogen via the radioresponse of the mouse ovary. We will follow lung cancer in mice with lower estrogen to determine the impact on ovarian function and risk for radiation-induced lung cancer. We may also consider estrogen replacement to determine how "hormone replacement" alters lung cancer risk from radiation exposure. 2) GC4419 is a radioprotector for radiation-induced mucositis and lung fibrosis from radiation exposure. What is not known, although the preliminary evidence suggests it could, is whether GC4419 has anti-carcinogenic effects. If it does, the potential to reduce the risk for cancer in humans after environmental or diagnostic radiation exposures is compelling.
Task Progress:	In pursuit of the aims of this project we will sample normal lung tissue, plasma, and tumors from irradiated or not cohorts of BALB/c mice. These tissue samples will be subject to histologic, gene, and miRNA expression, the presence of circulating miRNA, and copy number variation analysis in the context of sex differences as well to determine if there is a bio-signature indicative of sex differences. Immune histochemistry for estrogen signaling will be carried out to confirm gene or miRNA expression data associated with hormonal signaling. To date we have carried out irradiations in 13 of 21 cohorts. We have now irradiated our gamma-ray cohorts at 0.4, 0.75, and 1.5 Gy (females) and our 0.75 Gy cohort of male mice, or Si irradiations at 0.1, 0.2, and 0.4 Gy (male and female) and our Galactic Cosmic Radiation simulation beam (GCRsim) at 0.2 and 0.75 Gy (male and female). In total, including controls, 2,940 mice has been entered into the study. Unfortunately, with the severity of the COVID-19 pandemic in NY we were not able to carry out the Spring 2020 run and as such we were not able to complete the GCR cohorts and could not start the examination of our potential countermeasure. We tried to move the Spring run to the Summer run of 2020 but were not able to schedule this due to the COVID-19 pandemic. Tissues and serum from 94 animals have been collected for omics analysis as we have passed the 6 and 12 month point for several cohorts. Potential tumor tissue has been isolated and processed from 150 subjects. Suspected tumors are now developing. Furthermore, as a number of animals have become cachexic, currently 28, it is likely that they too have cancers for which total necropsies will be performed to identify tumors not found overtly. As we are nearing completion of Year 2, some progress is in the numbers of animals irradiated although we are now behind schedule given the impact of COVID-19. Histologic samples and veterinary examination of potential tumors is ongoing. Omics data will not be processed until late Year 3/Year 4 as many of these endpoints require collection only and are processed at a later time to avoid “batch effects” associated with sample processing. As it stands we are about 65% of the way through the animal cohorts.
Bibliography Type:	Description: (Last Updated: 12/14/2023)