Fiscal Year:	FY 2018	**Task Last Updated:**	FY 04/30/2018
PI Name:	Weil, Michael Ph.D.		
Project Title:	NSCOR: NASA Specialized Center of Research on Carcinogenesis		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
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:	80521-2807	**Congressional District:**	4
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-NSCOR Radiation
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No. of Post Docs:		**No. of PhD Degrees:**	1
No. of PhD Candidates:	4	**No. of Master' Degrees:**	0
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	4	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
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Task Description:	The proposed Carcinogenesis NASA Specialized Center of Research (NSCOR) addresses several key questions for the assessment of radiation risk. The NSCOR consists of four interrelated projects. Project 1 is a biomarker discovery study using integrative “omics” approaches over multiple levels of biological organization and involving multiple species. Biomarkers predictive of the outcomes of HZE (high energy) ion exposures can be used to extrapolate findings in mice to other species, including humans, that are most relevant to NASA’s exploratory missions. The biomarkers are also critical for understanding underlying carcinogenic mechanisms, early disease detection, and subsequent countermeasure development. Project 2 investigates qualitative differences in tumor progression and metastasis between HZE ion- and gamma ray-induced tumors. Project 3 examines the critical question of risk from protracted exposures to high LET (linear energy transfer) radiation at low doses and dose rates. To estimate the carcinogenic effects of these scenarios, we will use chronic exposures to high LET associated neutron radiation as a surrogate for conditions of space-relevant fluence rates and total doses. Project 4 utilizes the resources (irradiated mice and “omics” results) generated in the first three projects to study the neurobehavioral consequences of HZE ion and neutron exposures and whether they are related to tumorigenesis-related outcome measures and predicted by the same or distinct biomarkers. Two addenda were added to the NSCOR in the April 2017 – March 2018 reporting period. The first was designed to determine if a low dose aspirin regimen could be an effective countermeasure to high LET radiation-induced hepatocellular carcinoma. Two exposure conditions are included, and acute exposure to 0.2 Gy 300 MeV 28Si ions and a chronic exposure to 0.4 Gy of 252Cf neutrons. The second was designed to compare fractioned exposures to a simulated GCR (galactic cosmic radiation) beam to an acute exposure for the induction of hepatocellular carcinoma.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Accurately determining the cancer risk from high energy, charged particle radiation exposure is of great importance for designing human spaceflight missions, but it is becoming increasingly important for cancer radiotherapy as well. Radiation oncology appears poised to transition to charged particle radiotherapy in the form of proton therapy and carbon ion therapy. However, one of the risks of treating cancer with charged particle radiation is that the treatment itself can result in a new cancers, known as a second malignant neoplasms (SMN) (commonly used photon radiotherapy also increases SMN risk). The radiotherapy equipment and the patient treatment plans are designed to minimize SMN, but the models to predict risks from various exposures rest on some of the same assumptions about how charged particle radiation causes cancer that are being tested in this NSCOR grant. The results obtained in this program can be used to improve the design of treatment protocols and thus reduce the risks of SMN in radiotherapy patients.
Task Progress:	In Project 1, we collected serum, plasma, tissue samples and feces for the six and 12 month time points, and completed the gamma-H2AX assay on 32 of the fibroblast cultures established from 316 irradiated F2 mice. We found an expected and encouraging level of interindividual variance in double strand break (DSB) repair efficacies. We tested the directional genomic hybridization probes for mouse chromosomes 1 to 4 and found that they are not well suited as an exposure biomarker. We began to quantify miR-122-3p in the parental strains based on results obtained with archival samples in project 2. While the results are preliminary, we are seeing strain and sex differences in miR-122-3p levels. We are currently expanding the screening circulating miRNA profiles at various time points after radiation using molecular barcoding and next generation sequencing. The preliminary data indicated high correlation of NGS and qPCR results. In Project 2, gene expression profiles were re-analyzed using pathologically confirmed archival samples. The analysis identified common signaling pathways in high-LET induced, low-LET induced, and spontaneous hepatocellular carcinoma (HCC). These include activation of PI3K/AKT and suppression of PTEN (phosphatase and tensin homolog deleted from chromosome 10) signaling, which are also the molecular mechanisms in human HCC. Other identified signaling pathways are highly involved in ROS (reactive oxygen species) signaling, inflammatory responses, cell proliferation, and apoptosis. Despite the common molecular pathways, a subset of genes including 815 probes emerged as a signature to separate not only tumor and non-tumor, but also radiation-type in each group. The signature does not have a statistically significant pathway enrichment. We are currently investigating the driver genes and functional impact of this signature on different types of HCC. We completed experimental metastasis studies with MMTV-PyMT mice and continued studies with Afp-mCherry mice. In the MMTV-PyMT model, we found that high LET exposures do not increase metastatic efficacy. Ninety Afp-mCherry mice were irradiated or sham irradiated at NASA Space Radiation Laboratory (NSRL). These mice are used to study HCC metastasis to the lung. The mice are being monitored for circulating tumor cells, and some have been sacrificed 3 months post-irradiation to detect the earliest stages of tumorigenesis using newly developed tissue clearing and optical approaches. Project 3 involves the commissioning of a neutron irradiator in a shielded vivarium that meets the animal care requirements for long term mouse housing. Over the past year we renovated the building, calculated the activity of radioactive material required, and acquired the source and the irradiator. In Project 4, we are determining the effects of space radiation on brain function by performing neurobehavioral tests on mice exposed to simulated space radiation or neutron radiation. This year we completed the behavioral and cognitive testing at three time points following 28Si irradiation (300 MeV/n, 0.2 Gy): 1, 6, and 12 months. A striking observation was that irradiated BALB/c mice and irradiated F2 mice showed more hippocampus-contextual fear memory and a wider range in individual variability in contextual fear memory than irradiated C3H mice. The cognitive data illustrate the individual performance differences in 28Si ion-irradiated mice, especially in irradiated F2 mice and data support the potential to identify biomarkers for radiation-induced cognitive deficits. Eight mice of each treatment and sex were sacrificed and pertinent brain regions dissected for lipidomics analyses in the laboratory by Dr. Mark Emmett at University of Texas Medical Branch (UTMB). 192 samples were extracted and 191 (one sample was lost) were analyzed for comprehensive lipid composition by ultra high-resolution mass spectrometry methods. All samples were block randomized for consistency. Data analysis is in progress. In addition, Dr. Michael Story at UTSW (University of Texas Southwestern Medical Center) is analyzing plasma miRNA in the same mice. Finally, we are assessing levels of some specific markers shown to be sensitive to effects of aging and space radiation on the brain. In addition to the study described above, an independent cohort of C3H male mice were tested 6 months following 28Si ion irradiation as part of an aspirin treatment study. The dose of aspirin used has CNS (central nervous system) effects in C3H/HeNCrl mice. This is an important finding as the dosing was based on

	aspirin studies in C57BL/6J mice. We are currently analyzing these data and consider testing at later time points. For the addenda, we irradiated the mice for the acute 28Si exposure condition in the aspirin countermeasure study. The chronic neutron exposures are scheduled to begin in mid-May or early June of 2018. Work on the GCR simulator addendum is slated to begin in November of 2018 (NSRL-18C).
Bibliography Type:	Description: (Last Updated: 09/27/2023)
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