Fiscal Year:	FY 2020	**Task Last Updated:**	FY 10/29/2020
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
Start Date:	06/01/2015	**End Date:**	05/31/2022
No. of Post Docs:	0	**No. of PhD Degrees:**	2
No. of PhD Candidates:	6	**No. of Master' Degrees:**	0
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 5/31/2022 per NSSC information (Ed., 3/3/2020)		
Key Personnel Changes/Previous PI:	April 2020 report: Dr. Thamm has completed his role on the NSCOR. April 2019 report: Dr. Robert L Ullrich has transitioned from NSCOR Co-Director to Consultant ; Dr. Michael D. Story now serves as the Co-Director.		
COI Name (Institution):	Borak, Thomas Ph.D. (Colorado State University) Emmett, Mark Ph.D. (University Of Texas, Galveston) Hwang, Tae Hyun Ph.D. (University of Texas Southwestern Medical Center at Dallas) Ray, F. Andrew Ph.D. (Colorado State University) Bacher, Jeff Ph.D. (Promega Corporation) Halberg, Richard Ph.D. (University of Wisconsin, Madison) Raber, Jacob Ph.D. (Oregon Health & Science University) Story, Michael Ph.D. (University of Texas Southwestern Medical Center at Dallas) Ullrich, Robert Ph.D. (University of Texas, Galveston) Brandl, Alexander (Colorado State University)		
Grant/Contract No.:	NNX15AK13G		
Performance Goal No.:			

Performance Goal Text:	
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 performed next generation sequencing (NGS) to measure the levels of circulating miRNA in plasma of C3H mice that developed radiation-induced hepatocellular carcinoma (HCC) or spontaneous HCC. We have also sequenced non-tumor-bearing C3H mice as control. Our analysis indicated that a substantial number of miRNAs exhibited differences in plasma levels between tumor-bearing and non-tumor bearing groups. We compared the mouse data with 12 human HCC circulating miRNA markers published in Nature Scientific Reports, 2019 [Jin, Y., Wong, Y.S., Goh, B.K.P. et al. Circulating microRNAs as Potential Diagnostic and Prognostic Biomarkers in Hepatocellular Carcinoma. Sci Rep 9, 10464 (2019)]. Excluding 2 miRNAs that do not present in mice, we found all of the 10 miRNAs were significantly increased in HCC-bearing mice. We have also performed NGS profiling of circulating miRNA using samples that consist of time-series of irradiated F2 (C3H x BALB/c) mice that eventually developed HCC. We finished sequencing in March and the data analysis is ongoing. We expect that analysis from F2 data will validate the results of the C3H cohort and will determine whether we can identify early diagnostic markers of HCC in precancerous stage. In Project 2, we performed comparative analysis of gene expression profiles between mouse and human HCC. The human HCC gene expression profile was obtained from The Cancer Genome Atlas (TCGA) published data in Cell. 2017 Jun 15; 169(7):1327–1341.e23. Our analysis identified subgroups of human HCC patients that resembled gene expression of high-LET radiation-induced HCC or low-LET radiation-induced / spontaneous HCC in mouse model. The high-LET HCC group showed better survival in Kaplan-Meier analysis and were enriched with more tumor-infiltrating immune cells that function as tumor suppressors when compared with other types of HCC. We also developed and validated the C3H Afp-mCherry mouse model for HCC. This model consists of the C3H susceptible strain with the addition of an mCherry fluorescent reporter driven by the alpha fetoprotein (Afp) promoter. The reporter is designed to fluorescently label cancer cells for simple and unambiguous identification of liver tumors and metastasis. Using this mouse model, we have identified biomarkers for early detection of liver disease, many of which are also established biomarkers used for diagnosis of human liver disease (e.g., AFP and ALT). Cholesterol and albumin serum biomarkers were elevated in an HCC specific manner, a finding in humans that indicates a steatohepatitic HCC subtype. Interestingly, the vast majority of HCCs observed in the C3H Afp-mCherry congenic mice are of the steatohepatitic subtype. HCC prognosis is rather poor due to late diagnosis and poor sensitivity of current testing methods. We have shown that elevated plasma AFP is capable of identifying mice that will eventually develop HCC, at least 6 months in advance of when tumors are typically detectible in C3H mice. In combination with other biomarkers being identified in this NSCOR, there is the potential to develop a panel of biomarkers for a minimally invasive blood test to identify early stage liver disease in mice that could potentially be translatable for use in humans. Lung lesions arising in our irradiated mice are currently being examined to determine if they are metastasized from the liver. Results of these analyses will help us answer the question of whether there is an increased HCC malignancy from HZE Ions. In Project 3, we calculated survival data for C3H male and BALB/c female mice irradiated with 252Cf neutrons at low dose rate (1mGy/day). Histopathology review on these groups is in progress. In Project 4, BALB/c and C3H female and male mice and their F2 hybrid progeny were irradiated with 28Si ions (350 MeV/n, 0.2 Gy) and tested for behavioral and cognitive performance 1, 6, and 12 months following irradiation. The plasma of the mice was collected for analysis of miRNA levels. Select, pertinent brain regions were dissected for lipidomics analyses and analyses of levels of select biomarkers shown to be sensitive to effects of space radiation in previous studies. We analyzed the relationships between behavioral and cognitive measures, plasma miRNAs, lipid in pertinent brain regions, and biomarkers in brain sensitive to effects of radiation in previous studies. A manuscript with these data is currently being finalized. The miRNA expression patterns developed in Project 1 have been applied to the endpoints for cognitive function being developed in Project 4. There are numerous miRNA, already identified as associated with a number of psychologic

	disturbances, fear for example, whose expression is altered in mice responding to different cognitive stimuli. These data are being analyzed now. Raw lipid data sets collected on the brain samples provided by Dr. Raber have been recompiled with a s/n of 5:1. These files were sent to Dr. Raber's group on 3/5/2020 and his computational mathematician (Jessica Minnier) is analyzing the data now. When complete we will correlate to the lipid i.d.s and determine biological significance correlated to the behavioral data. Two Addenda were in progress during the period covered by this report: a study of low dose aspirin as a radiation countermeasure and a comparison of the effects of acute exposure and fractionated exposure to GCRsim. We saw no difference in either survival or tumor-free survival for mice on a low dose aspirin regimen during and following acute 28Si ion exposure. A similar study of aspirin efficacy against low dose rate neutron exposure is in progress. Major Milestones (April 2019 – March 2020) - A new mouse model for HCC has been developed and validated for studying HCC. 264 F1 and 264 C3H Afp-mCherry congenic male and female mice have been irradiated and blood samples collected at 3 to 6 month intervals and liver and lung tissues at terminal collections (21 to 24 months post irradiation). - We have shown that the new mouse model containing the mCherry reporter for labeling cancer cells allows for unambiguous identification of liver tumors and metastases. - Plasma and tumor biomarkers have been identified that detect liver disease can predict the development of HCC before any visible sign of a tumor using simple blood tests. - Low dose rate (1 mGy/day) neutron irradiation leads to dose dependent life shortening in female mice. - A low dose aspirin regimen dose not improve overall survival or tumor-free survival following acute 28Si ion exposure. - Plasma miRNAs that distinguish between tumor-bearing and non-tumor mice have been identified.
Bibliography Type:	Description: (Last Updated: 09/27/2023)
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