Fiscal Year:	FY 2021	**Task Last Updated:**	FY 07/23/2021
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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City:	Fort Collins	**State:**	CO
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:	4	**No. of Master' Degrees:**	0
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	6	**Monitoring Center:**	NASA JSC
Contact Monitor:	Elgart, Robin	**Contact Phone:**	281-244-0596 (o)/832-221-4576 (m)
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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 Ph.D. (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 found significant overlap of circulating miRNA markers associated with hepatocellular carcinoma (HCC) in humans and mice which supports the feasibility of using the C3H mouse model to develop markers for human disease. Our results from assaying these circulating miRNA markers in a precancerous stage of radiation-induced HCC suggest that they can be used to monitor potential cancer risk during or after spaceflight. Furthermore, they may also be used to monitor high risk individuals for HCC. The integrated transcriptome analysis of mouse HCC samples suggests that high-LET and low-LET radiation induced different molecular subtypes of HCC. These can be correlated with distinct subtypes of human HCCs that have significant differences in clinical outcome. These results have been accepted for publication in Scientific Reports (Ed. note 7/25/21: now published--see Bibliography for Ding et al.). In Project 2, we found no evidence that high LET radiation exposure leads to enhanced metastatic potential in ether of the two model systems tested. However, we did identify serum biomarkers for preclinical detection of hepatocellular carcinoma. These results have been published online in the International Journal of Radiation Biology (see Bibliography section for Udho et al.). In Project 3, we calculated survival data for C3H male and BALB/c female mice that received acute exposures to 0.4 Gy of neutrons and compared those results to mice of the same strain and sex irradiated with 0.4 Gy of neutrons at low dose rate (1mGy/day). Acute exposure led to considerable life shortening in female BALB/c mice with a small improvement in survival if the same dose is delivered at low dose rate. In male C3H mice there is also considerable life shortening from the acute exposure, but low dose rate sparing is substantial. Whether the greater detrimental effect of the low dose rate exposure in BALB/c female mice compared to male C3H mice is due to the strain difference or the sex difference is unknown. Note that these results are for overall survival out to 800 days of age; histopathology review of the tumors that arose in these groups is in progress. In Project 4, Drs. Raber, Emmett, and computational expert Jessica Minnier focused on analyzing the lipid data sets which had been recompiled with a s/n of 5:1. Drs. Emmett and Yu (University of Texas Medical Branch-UTMB) then assigned lipid i.d.s to the significant m/z values identified by computational analysis. Further correlations were made between the behavioral data (Dr. Raber), the miRNA data (Dr. Story), and the lipid data (Dr. Emmett). At this point, biological correlations between all data sets were assigned. The results were reported in the manuscript entitled: "Associations between lipids in selected brain regions, plasma miRNA, and behavioral and cognitive measures following 28Si ion irradiation," which has been published online in Scientific Reports (see Bibliography section for Minnier et al.). 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 observed no difference in survival between male C3H mice that received acute GCRsim exposures and those that received fractionated exposures.
Bibliography Type:	Description: (Last Updated: 09/27/2023)
Articles in Peer-reviewed Journals	Udho EB, Huebner SM, Albrecht DM, Matkowskyj KA, Clipson L, Hedican CA, Koth R, Snow SM, Eberhardt EL, Miller D, Van Doorn R, Gjyzeli G, Spengler EK, Storts DR, Thamm DH, Edmondson EF, Weil MM, Halberg RB, Bacher JW. "Tumor aggressiveness is independent of radiation quality in murine hepatocellular carcinoma and mammary tumor models." Int J Radiat Biol. 2021 Mar 31:1-12. Published online: 31 Mar 2021. https://doi.org/10.1080/09553002.2021.1900946 ; PMID: 33720813 , Mar-2021

Articles in Peer-reviewed Journals	Minnier J, Emmett MR, Perez R, Ding LH, Barnette BL, Larios RE, Hong C, Hwang TH, Yu Y, Fallgren CM, Story MD, Weil MM, Raber J. "Associations between lipids in selected brain regions, plasma miRNA, and behavioral and cognitive measures following 28Si ion irradiation." Sci Rep. 2021 Jul 21;11(1):14899. https://doi.org/10.1038/s41598-021-93869-3 ; PMID: 34290258; PMCID: PMC8295277 , Jul-2021
Articles in Peer-reviewed Journals	Zimmerman B, Kundu P, Rooney WD, Raber J. "The effect of high fat diet on cerebrovascular health and pathology: A species comparative review." Molecules. 2021 Jun 4;26(11):3406. Review. https://doi.org/10.3390/molecules26113406 ; PMID: 34199898; PMCID: PMC8200075 , Jun-2021
Articles in Peer-reviewed Journals	Raber J, Fuentes Anaya A, Torres ERS, Lee J, Boutros S, Grygoryev D, Hammer A, Kasschau KD, Sharpton TJ, Turker MS, Kronenberg A. "Effects of six sequential charged particle beams on behavioral and cognitive performance in B6D2F1 female and male mice." Front Physiol. 2020 Aug 28;11:959. https://doi.org/10.3389/fphys.2020.00959 ; PMID: 32982769; PMCID: PMC7485338 , Aug-2020