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| **Fiscal Year:** | FY 2019 | **Task Last Updated:** | FY 04/08/2019 |
| **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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| **PI Address 2:** | 1618 Campus Delivery | | |
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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:** | 05/30/2020 |
| **No. of Post Docs:** | 6 | **No. of PhD Degrees:** | 0 |
| **No. of PhD Candidates:** | 1 | **No. of Master' Degrees:** | 0 |
| **No. of Master's Candidates:** | | **No. of Bachelor's Degrees:** | 0 |
| **No. of Bachelor's Candidates:** | 3 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Simonsen, Lisa | **Contact Phone:** | |
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| **Flight Program:** | | | |
| **Flight Assignment:** | | | |
| **Key Personnel Changes/Previous PI:** | 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 )<br>Emmett, Mark Ph.D. ( University Of Texas, Galveston )<br>Hwang, Tae Hyun Ph.D. ( University of Texas Southwestern Medical Center at Dallas )<br>Liber, Howard Ph.D. ( Colorado State University )<br>Ray, F. Andrew Ph.D. ( Colorado State University )<br>Thamm, Douglas V.M.D. ( Colorado State University )<br>Bacher, Jeff Ph.D. ( Promega Corporation )<br>Halberg, Richard Ph.D. ( University of Wisconsin, Madison )<br>Raber, Jacob Ph.D. ( Oregon Health & Science University )<br>Story, Michael Ph.D. ( University of Texas Southwestern Medical Center at Dallas )<br>Ullrich, Robert Ph.D. ( University of Texas, Galveston ) | | |
| **Grant/Contract No.:** | NNX15AK13G | | |
| **Performance Goal No.:** | | | |

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| **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.<br>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:** | For Project 1, we collected tissue samples of lung, liver, amygdala and hypothalamus, along with serum, plasma, and feces from the unirradiated and 28Si irradiated parental strains (BALB/c and C3H). Lipid profiling was completed on the liver, lung, amygdala, hypothalamus, and serum samples from all post-irradiation time points (1, 6, 12, and 18 months). Circulating miRNA from blood plasma was analyzed at 1, 6, and 12 months. 18 month plasma samples were not collected. Strain appears to be the largest factor in characterizing the miRNA found in blood plasma, followed by time post-irradiation. Sex is but a modest factor of variation. The presence of 87 miRNA can be partitioned into 15 clusters based upon their presence at a given time. These patterns can be used to develop predictors for hepatocellular carcinoma (HCC) risk and then applied across the F2 mice as validation.<br>We monitored the F2 mice until they became moribund or reached 800 days of age. All of the F2 mice have now been necropsied and any tissue lesions detected were prepared for histopathology. Histopathology has been completed on about half of these mice.<br><br>In Project 2, we completed the sample collection from the (B6C3H)F1 Tg::Apf-mCherry mice. Liver and lung tissue sections were examined by a pathologist and we have found a variety of pathologies in the liver (HCC, dysplastic nodules, hepatitis, and steatosis) and lung (peribronchial chronic inflammation and carcinoma), though no major difference among treatment groups (sham, gamma-irradiated, and silicon-irradiated) was observed. Our mouse model was validated and found to be an excellent model for detecting early alpha fetoprotein (AFP) expression in liver disease as well as for unambiguous identification of metastasis from the liver to other tissues. Among the approximately 30 measurements obtained from plasma and whole blood (liquid biopsy-accessible measurements), we have found AFP and alanine aminotransferase (ALT) to be good predictors of the presence of liver disease (sensitivity 60-70%, specificity 85-90%).<br><br>Our second cohort of mice, the C3H Tg::Afp-mCherry, which also include a pilot study with the radioprotectant PrC-210, were irradiated a tNASA Space Radiation Laboratory (NSRL) NSRL18A and we completed plasma collections at two timepoints (6 and 9 months post irradiation) for our longitudinal study.<br><br>Also ongoing in Project 2 is the genomic and epigenomic characterization of HCC tumors in C3H mice. At this juncture we have started to develop approaches that use other HCC data sets from mice based upon exposures to chemicals (7 datasets) or in genetically engineered mouse strains (4 datasets) to compare to low LET, high LET, or spontaneous tumors generated in the prior NSCOR. Furthermore, we have begun making comparisons of these mouse datasets to datasets for human HCC.<br><br>In Project 3 we completed the low dose rate neutron irradiations and performed acute neutron exposures at Columbia University. We also completed low dose neutron exposures of mice and rats for the CNS (central nervous system) NSCOR, rats for a cardiovascular effects study (Marjan Boerma, Principal Investigator-PI), and mice for an in utero effects study (Jon Steller, PI). The facility is currently being used to irradiate mice for the GI (Gastronintestinal) NSCOR (Albert Fornace, PI), and for a countermeasure addendum and an immunological effects pilot study. In Project 4, we finalized behavioral and cognitive testing of BALB/c, C3H, and F2 mice 1, 6, and 12 months following acute 28Si ion irradiation. At the three time points, plasma was collected for miRNA analyses by Dr. Story’s laboratory at UTSW (University of Texas Southwestern Medical Center) (Project 1). At the three time points, selected mice of the parental strains were sacrificed by cervical dislocation and their hypothalamus and amygdala dissected. The tissues of one hemisphere were analyzed for lipidomics by Dr. Emmett’s laboratory at UTMB (University of Texas Medical Branch at Galveston). Six lipid measures of the mice from the three time points were analyzed. From the hypothalamic and amygdaloid tissues of the other hemisphere, ELISAs were performed to assess levels of the specific biomarkers. For the parental strains, we compiled a large excel file with all the behavioral data for the open field, object recognition, and contextual and cued fear learning and morning, all the plasma miRNA data, and the lipidomics data on the six lipids. The |

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| | data are currently analyzed for several manuscripts. This year, we also performed a countermeasure study with aspirin. An independent cohort of C3H male mice were tested 6 and 18 months following 28Si ion irradiation as part of an aspirin treatment study. In addition, we started to behaviorally test C3H and BALB/c mice as part of Project 3, following chronic neutron exposure. Mice were tested at 600 days of age in March of 2019. The data are currently being analyzed.<br><br>For the Addenda, we began neutron irradiation of mice for the low dose rate arm of the aspirin countermeasure study. We irradiated mice for the GSAM (Galactic Cosmic Ray Simulation and Mitigation) study in November of 2018 (NSRL-18C). 135 male C3H mice were irradiated with 0.4 Gy of simulated GCR split into 19 fractions delivered over 4 weeks. An additional 135 mice received an acute exposure of 0.4 Gy.<br><br>Major Milestones (April 2018 – March 2019)<br><br>* Lipid data completed for liver, lung and serum for all time points (1, 6, 12 and 18-momth) for Project 1.<br><br>* Completed necropsies and histopathology slide preparation for all F2 mice in Project 1.<br><br>* Completed low dose rate neutron exposures for Project 3 and performed acute neutron exposures at Columbia University.<br><br>* Provide low dose rate neutron exposures for several NASA funded investigators.<br><br>* Lipid data completed for amygdala and hypothalamus samples for all time points provided for Project 4.<br><br>* Irradiated mice at NSRL for the GSAM study.<br><br>* Began the low dose rate exposure aspirin countermeasure study.<br><br>* Completed behavioral and cognitive testing of BALB/c, CRH, and F2 mice 1, 6, and 12 months following acute 28Si ion irradiation, along with plasma miRNA, brain lipidomics on 6 lipids.<br><br>* Completed behavioral testing of mice treated with aspirin as a contermeasure.<br><br>* Completed behavioral testing of C3H and BALB/c following chronic neutron exposure at 600 days of age. |
| **Bibliography Type:** | Description: (Last Updated: 09/27/2023) |
| **Abstracts for Journals and Proceedings** | Weil MM, Ullrich RL, Ding L, Emmett M, Yu Y, Bacher JS, Halberg R, Raber J, Edmondson EF, Ray FA, Thamm D, Borak T, Story MD. "Carcinogenesis NSCOR Overview and Dose-Rate Effects." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |
| **Abstracts for Journals and Proceedings** | Weil MM. "Approaches to understanding space radiation cancer risks." Joint session at Radiation Research Society Annual Meeting and Conference on Radiation and Health Meeting. 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018.<br>64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. , Sep-2018 |
| **Abstracts for Journals and Proceedings** | Halberg R. "Mechanisms Underlying Increased Malignancy from Space Radiation." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |
| **Abstracts for Journals and Proceedings** | Raber J, Turker M, Impey S. "A general space radiation synaptic signature in hippocampus following proton, 56Fe, and 28Si ion irradiation." Session; F2.2: Space Radiation Risk and Countermeasures: Physical and Biophysical Mechanisms, Modelling and Simulations. Committee on Space Research (COSPAR) 2018 42nd Scientific Assembly, Pasadena, CA, July 14-22, 2018.<br>Committee on Space Research (COSPAR) 2018 42nd Scientific Assembly, Pasadena, CA, July 14-22, 2018. , Jul-2018 |
| **Abstracts for Journals and Proceedings** | Kronenberg A, Gauny S, Gygoryev D, Fuentes Anaya A, Lee J, Torres ERS, Boutros S, Turker M, Raber J. "GCR simulation studies with human and mouse models." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |
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| **Abstracts for Journals and Proceedings** | Borak TB, Krumland N, Phillips P, Weil MM. "A Facility to Investigate Health Effects from High LET Radiation at Space-Relevant Dose Rates and Total Exposures." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |
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| **Abstracts for Journals and Proceedings** | Bacher J, Udo E, Halberg R, Raber J, Perez R, Emmett MR, Ullrich RL, Ding L, Ray FA, Story MC, Weil MM. "Carcinogenesis NSCOR: Mechanisms Underlying Increase Hepatocellular Carcinoma Malignancy from Space Radiation." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |

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| **Abstracts for Journals and Proceedings** | Ray FA, Fallgren CM, Weil MM. "GSAM Project: Feasibility of an Extended Fractionation Exposure." 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019.<br>2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019 |
| **Articles in Peer-reviewed Journals** | Ochola DO, Sharif R, Bedford JS, Keefe TJ, Kato TA, Fallgren CM, Demant P, Costes SV, Weil MM. "Persistence of gamma-H2AX foci in bronchial cells correlates with susceptibility to radiation associated lung cancer in mice." Radiat Res. 2019 Jan;191(1):67-75. Epub 2018 Nov 6. https://doi.org/10.1667/RR14979.1 ; PubMed PMID: 30398394 , Jan-2019 |