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<td>PI Name:</td>
<td>Weil, Michael Ph.D.</td>
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<td>Project Title:</td>
<td>NSCOR: NASA Specialized Center of Research on Carcinogenesis</td>
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<td>PI Email:</td>
<td><a href="mailto:michael.weil@colostate.edu">michael.weil@colostate.edu</a></td>
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<td>Simonsen, Lisa</td>
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<td>Key Personnel Changes/Previous PI:</td>
<td>Borak, Thomas Ph.D. (Colorado State University)</td>
<td>Emmett, Mark Ph.D. (University Of Texas, Galveston)</td>
<td>Hwang, Tae Hyun Ph.D. (University of Texas Southwestern Medical Center at Dallas)</td>
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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.

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.

This is the first year of funding, so much of the work to date has been logistical to prepare for mouse irradiations. We have arranged for beam time at NASA Space Radiation Laboratory (NSRL) in Fall 2016 and secured approval from 4 different institutions for the use of mice in the experiments. Because some of the strains of mice needed are not commercially available in sufficient numbers, we have established breeding colonies for them at Colorado State University and the University of Wisconsin.

In Project 1 we have optimized a lipidomic screen for use with mouse samples. In Project 2 we have reviewed the pathology on 210 cases of mouse hepatocellular carcinomas (HCC) and characterized them for histological features that may be relevant to their propensity to metastasize to the lung, including fibrosis, local invasion, vascular invasion, cellular and nuclear pleomorphism, tumor subtype, and mitotic index. One feature, high microvessel density, appears to be more common in metastatic HCC. We have also begun to look for mutations in the tumors by sequencing DNA from five of them (whole exome sequencing). We have detected mutations in these tumors that are also common in human HCC.

Project 3 requires us to install a neutron irradiator in a heavily shielded building that also meets the animal care requirements for long term mouse housing. We have secured a suitable building and begun the process of renovating it. We are also drawing up the specifications for the radioactive source in the neutron irradiator.

For Project 4 we have identified the neurobehavioral assays that will be most sensitive to radiation effects.
