Fiscal Year:	FY 2021	**Task Last Updated:**	FY 01/15/2021
PI Name:	Chung, Caroline M.D.		
Project Title:	Quantitative Imaging and Biofluid Biomarkers Predictive of Neurocognitive Toxicity from Brain Irradiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	77030	**Congressional District:**	9
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	Directed Research
Start Date:	03/15/2019	**End Date:**	03/14/2022
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: Period of performance is now 3/15/2019-3/14/2022 per NSSC information since now goes through NSSC; original POP was 1/14/2019-1/13/2022 (Ed., 5/29/19)		
Key Personnel Changes/Previous PI:	Dr. Eric Sulman left MD Anderson in September, 2019 and Dr. Simona Shaitelman, Associate Professor in the Department of Radiation Oncology, MD Anderson Cancer Center, will assume oversight of the blood biomarkers work.		
COI Name (Institution):	Wefel, Jeffrey Ph.D. (Co-PI: University of Texas MD Anderson Cancer Center) Shaitelman, Simona M.D. (The University of Texas MD Anderson Cancer Center)		
Grant/Contract No.:	80NSSC19K0659		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	NASA is concerned about the functional consequences of inflight acute exposure to space radiation and the probability of radiation exposure enhancing or accelerating late neurodegenerative conditions post-mission. This proposed research aims to acquire data on neurocognitive/behavioral impairments and associated biomarkers observed in patients who are undergoing cranial exposure to ionizing radiation with an emphasis on non-invasive imaging modalities and serum biomarkers to quantify predictive changes linked to acute and late neurocognitive impairment and radiation dose. This work will provide benchmark data on structural and functional changes in patients resulting from photon (X-ray) and proton exposures during radiotherapy of head and neck and intracranial neoplasms. Existing research data suggest that animals and humans may share similar pathophysiological mechanisms following brain radiation exposure that lead to adverse cognitive or behavioral conditions or the exacerbation or acceleration of late degenerative conditions. To establish thresholds of permissible exposure for effects on the central nervous system, it is crucial to understand scaling relationships between humans and animals. In the proposed research, the broader range in radiation dose exposure in a more neurocognitively vulnerable population will facilitate more rapid signal finding investigations of these biomarkers that can be further refined for subsequent investigation in astronauts. There is complementary overlap between this work and proposed directed work at MD Anderson involving radiation-induced cardiotoxicities that will tie in common pathways between CVD (cardiovascular) and CNS (central nervous system) decrements through the investigation of common biomarkers. The gaps Degen-2 and -3 and CNS-1, -2, and -6 involve identification of adverse outcome pathways, progression rates and latency periods, and early surrogate markers for radiation-induced cardiovascular/cerebrovascular disease and early and late CNS decrements. Research deliverables from this work will help close the above gaps and serve as quantifiable measures of response to guide countermeasure development and validation in animal studies with HZE (high energy) exposures. Results will also drive predictive model development (Degen-5 and CNS-5). Specific Aims: Aim 1: In patients receiving proton and photon radiotherapy involving radiation exposure to the brain, evaluate serial multidimensional, multimodal tests of neurocognitive function (clinical neurocognitive testing and digital testing including NASA Cognition, CogState C3), biofluid biomarkers (including markers associated with vascular dysfunction and cardiotoxicity following radiation exposure), and quantitative multiparametric magnetic resonance imaging data. Aim 2: Identify brain subregions vulnerable to radiation toxicity using quantitative multiparametric magnetic resonance images that are associated with changes in neurocognitive function and characterize changes in specific neurocognitive domains in relation to radiation dosimetry. Aim 3: Establish predictive models of neurocognitive decline integrating clinical characteristics, quantitative multiparametric magnetic resonance imaging parameters, and biofluid biomarkers pre- and post-irradiation.
Rationale for HRP Directed Research:	Highly constrained research. Time constraint: There is insufficient time for competitive solicitation through a NASA Research Announcement (NRA) due to the Degen Risk accelerated schedule and milestone delivery. The early results from this clinical pilot study will be used in the formulation of the FY22 CVD/CNS NASA Specialized Center of Research (NSCOR) solicitation which needs to be released in early FY21 in order to meet our PRR (Path to Risk Reduction) schedule (which has the studies selected from the FY22 NSCOR commencing at the beginning of FY22). This NSCOR feeds into the 2026 PRR milestone of “Identify Late CNS Countermeasures.” Research constraint: This work is also highly constrained research involving a pilot study with human radiotherapy cohorts and the advanced imaging expertise available at MD Anderson. In addition to the FY22 NSCOR, the findings from this pilot study are expected to inform future solicited animal studies. Retrospective studies are not possible because the biomarkers are newly identified and are not yet fully validated, which this study will help to do.
Research Impact/Earth Benefits:	The consequences of radiation exposure to astronaut health during and after space flight remain unknown and the possibility of radiation exposure enhancing or accelerating neurodegenerative conditions is not well understood. This study aims to provide comprehensive data on structural, physical, and functional imaging changes in cancer patients whose brains were exposed to radiation as part of their cancer treatment. We will also investigate biomarker changes in these patients. We expect to identify changes in the brain and biomarkers, whilst also exploring the relationship between changes in the brain and radiation exposure to different sections of the brain. Our results will be used to identify potential non-invasive biomarkers that indicate neurocognitive decline, which can be used to identify brain disease in astronauts. The biomarkers may also serve as surrogates for future investigations of countermeasures to prevent neurocognitive decline following radiation exposure to the brain.
	In this prospective single-arm observational imaging study, patients undergoing intra-cranial (non-brain parenchyma) or head and neck radiation therapy will be identified in the Department of Radiation Oncology (N=50). After patients provide written informed consent, serial multiparametric MRI, assessments of cognitive function and blood samples will be collected at baseline, during radiation treatment, and 1, 3, 6, 12, and 24 months post-treatment. Initial Institutional Review Board (IRB) approval of the study was given on 2/14/2019 by MD Anderson. After completing addition administrative set up, including the activation meeting, the study was activated on 8/22/2019. The enrollment of patients in the trial was delayed following the study start due to several reasons including the following: 1. Contracts and acquisition of hardware for the cognitive assessments required time to complete. We have purchased hardware (i.e., a laptop and an iPad) to collect digital neurocognitive assessments from patients. We established a formal consulting agreement with Dr. Mathias Basner, an expert in NASA Cognition in astronauts and astronauts surrogate populations. The laptop was formally calibrated by Pulsar Informatics, Inc., for use with the NASA Cognition battery. We licensed Cogstate C3 and purchased equipment for this test. All digital testing platforms were installed and piloted on the devices. Dr. Wefel’s research team has been trained on all neurocognitive tests, devices, and measures used in this project, and has developed a laboratory protocol manual for the project. 2. One of the lead scientists involved moved to a different institution. This required another adjustment and re-approval of the study plan. A new collaborator, Dr. Simona Shaitelman, is conducting the biofluid collection an analysis. 3. While we were able to secure additional funding for the incorporation of novel and promising MRI technique (i.e.,

Task Progress:	rs-fMRI) for the evaluation of neurocognitive deterioration as part of the imaging biomarker assessment, this required re-approval of the amended study protocol by MD Anderson. 4. Enrollment of patients in the study was halted during COVID-19 pandemic (March-July of 2020). We resumed pre-screening activities in August 2020. Of note, while the pre-screening and trial enrollment is reactivated, the COVID-19 pandemic continues to impact study accrual as many patients are still preferring to have their clinical appointments carried out remotely through virtual visits, which prohibits eligible enrollment on this trial protocol. We have spent this additional time required for the listed items above to develop a workflow and establish a multi-departmental research clinical team to run this study. This required presentations at research meetings for the CNS and Head and Neck Radiation Oncology groups, the institutional IT team, the Radiation Oncology Biomarker working group, Diagnostic Radiology and Imaging Physics research meetings, and Neuropsychology research team. Additionally, we have developed databases for this trial protocol and a centralized imaging workflow, including the necessary software pipelines for image analysis. We also completed work around image analysis, including preclinical development work for the rs-fMRI portion of the project for which we received additional, complementary, independent funding. We established a network of connections of the brain using brain images of several patients and developed a network analysis of the connections. Radiotherapy dose maps were registered to the network and correlated with changes in the network metrics between different periods of time. This will be applied to future patient's brain images in this project. As of January 5th, 2021, we have pre-screened 20 patients and recruited and enrolled one patient in the study. We obtained baseline comprehensive neurocognitive testing, NASA Cognition testing, CogState C3 testing, and patient reported outcomes. We have likewise obtained all tests and PRO (patient-reported outcomes) during the on-treatment weekly visits with no deviations from the planned study calendar. We worked with Dr. Basner to review the initial NASA Cognition test results and data visualization to confirm this new technology was functioning as intended. We have reviewed, scored, and entered all data into our study specific database. In the past two years we have established the foundation to run this unique study at MD Anderson. We are now actively screening brain, and head and neck cancer patients to be enrolled in the IRB protocol associated with this project. Despite the delays caused by COVID-19 restrictions at MD Anderson, we anticipate successful enrollment of patients in year 3 of this project and complete enrollment by Spring 2022.
Bibliography Type:	Description: (Last Updated: 08/07/2023)
Abstracts for Journals and Proceedings	Mitchell D, Liu H, Shaitelman S, Phan J, Farhat M, Johnson J, Slack Tidwell R, Wefel J, Chung C. "Quantitative imaging and biofluid biomarkers predictive of neurocognitive toxicity from brain irradiation. " 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021