Fiscal Year:	FY 2022	**Task Last Updated:**	FY 08/07/2023
PI Name:	Chung, Caroline M.D.		
Project Title:	Imaging and Serum Biomarkers to Predict and Identify Early Cardiac Injury from Radiation Exposure		
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) **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		
PI Email:	CChung3@mdanderson.org	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	713-745-5422
Organization Name:	University of Texas MD Anderson Cancer Center		
PI Address 1:	1515 Holcombe Blvd.		
PI Address 2:	Radiation Oncology and Diagnostic Imaging		
PI Web Page:			
City:	Houston	**State:**	TX
Zip Code:	77030	**Congressional District:**	9
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	Directed Research
Start Date:	08/23/2018	**End Date:**	08/22/2023
No. of Post Docs:	1	**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
Contact Monitor:	Elgart, Robin	**Contact Phone:**	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 8/22/2023 per NSSC information (Ed., 2/7/23) NOTE: End date changed to 8/22/2022 per NSSC information (Ed., 10/14/21) NOTE: Period of performance is now 8/23/2018-8/22/2021 per NSSC information since now the project goes through NSSC (Ed., 5/29/19)		
Key Personnel Changes/Previous PI:	June 2020 report: Added Dr. Jun-ichi Abe as CoInvestigator (CoI) and removed Dr. Saumil Gandhi as CoI.		
COI Name (Institution):	Dabaja, Bouthaina M.D. (Co-PI: University of Texas MD Anderson Cancer Center) Lopez-Mattei, Juan M.D. (University of Texas MD Anderson Cancer Center) Swamique, Yusuf M.D. (University of Texas MD Anderson Cancer Center) Gladish, Gregory M.D. (University of Texas MD Anderson Cancer Center) Lin, Steven M.D., Ph.D. (Co-PI: University of Texas MD Anderson Cancer Center) Layman, Rick Ph.D. (University of Texas MD Anderson Cancer Center) Abe, Jun-ichi M.D., Ph.D. (University of Texas MD Anderson Cancer Center)		
Grant/Contract No.:	80NSSC18K1639		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	[ED. NOTE November 2018: Principal investigator (PI) changed to Dr. Caroline Chung, from Dr. Sarah Milgrom, due to Dr. Milgrom's change in institution. Period of performance also revised to 8/23/2018-8/22/2021, due to PI change; original period of performance was 7/18/2018-9/30/2021.] Within the "Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure and Secondary Spaceflight Stressors," the gaps Degen-2 and -3 involve identification of adverse outcome pathways, progression rates and latency periods, and early surrogate markers for radiation-induced cardiovascular disease. To date, no tasks have included human radiotherapy cohorts to assess those parameters and identify biomarkers. The proposed work will acquire data on cardiovascular impairments and associated biomarkers observed in patients undergoing cardiac exposure to ionizing radiation with emphasis on non-invasive imaging modalities to quantify predictive changes linked to late impairment. Prompt identification of damage may enable interventions to prevent progression to cardiac dysfunction. Furthermore, study of cardiac changes that occur during and soon after radiotherapy would grant insight into the pathophysiology, which may lead to novel therapeutic interventions. The results may then be correlated with other studies performed in animals or in human cohorts with different types of radiation exposure such as astronauts. Research deliverables from this work will help close gaps Degen-2 and -3 as well as feed into countermeasure development and validation in animal studies with space radiation exposures. Results will also drive predictive model development (Degen-5). Specific Aims for the work include: 1) Assess for cardiac toxicity in patients treated with radiotherapy to the chest. 2) Assess for an association between 3D imaging findings suggestive of cardiac injury and radiation dosimetry. 3) Explore the association of radiation exposure with serum biomarker levels. Research Deliverables 1. Evaluation of MRI as noninvasive imaging modality for detection of early indicators of cardiotoxicity following radiotherapy, compared with electrocardiograms. 2. Evaluation of serum markers and other cardiovascular parameters for detection of early indicators of cardiotoxicity following radiotherapy.
Rationale for HRP Directed Research:	There is insufficient time for competitive solicitation through an NRA (NASA Research Announcement) due to Degen Risk accelerated schedule and milestone delivery. This work is also highly constrained research involving a pilot study with human radiotherapy cohorts and the advanced imaging expertise available at MD Anderson. 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:	Within the "Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure and Secondary Spaceflight Stressors," the gaps Degen-2 and -3 involve identification of adverse outcome pathways, progression rates and latency periods, and early surrogate markers for radiation-induced cardiovascular disease. To date, no tasks have included human radiotherapy (RT) cohorts to assess those parameters and identify biomarkers. The proposed work will acquire data on cardiovascular impairments and associated biomarkers observed in patients undergoing cardiac exposure to ionizing radiation with emphasis on non-invasive imaging modalities to quantify predictive changes linked to late impairment. Prompt identification of damage may enable interventions to prevent progression to cardiac dysfunction. Furthermore, study of cardiac changes that occur during and soon after RT would grant insight into the pathophysiology, which may lead to novel therapeutic interventions. The results may then be correlated with other studies performed in animals or in human cohorts, such as astronauts, with different types of radiation exposure. Research deliverables from this work will help close gaps as well as feed into countermeasure development and validation in animal studies with space radiation exposures. Results will also drive predictive model development. This study aims to identify early markers of cardiac injury after radiation exposure, at a time when steps could be taken to prevent progression to irreversible cardiac dysfunction. The results of this study may be correlated with other studies performed in animals or in human cohorts with different types of radiation exposure, such as astronauts during space travel, and the ultimate goal of our work is to develop agents that prevent cardiac toxicity through early detection and intervention.
Task Progress:	FY22 UPDATE (Ed., 9/28/23) To date, 38 patients have been identified and consented to the protocol PA16-0971 with at least one baseline imaging. However, only 24 patients have been considered evaluable if more than one imaging has been acquired. Due to the COVID-19 pandemic, the 7 months from March to October 2020 enrollment was halted and a number of post-scans and follow-ups were canceled; and patients withdrew from study due to the need for travel. Study fully reopened in October. Serum Biomarkers: Blood samples collected before, during and at the end of radiotherapy (RT) were processed for 17 patients. The p90RSK activity after H2O2 stimulation was significantly higher ($p=0.0015$) in the post-RT group, compared with both pre-RT and mid-RT groups. No significant difference was found among pre-RT and mid-RT groups and no significant difference was detected in basal p90RSK activity. Our preliminary results suggest that peripheral blood mononuclear cells (PBMCs) p90RSK is a potential early marker of endothelial injury from radiation therapy. Correlation of Imaging and Blood Biomarkers: Of the 24 patients registered to the study, baseline and matching post-radiation Cardiac MRI (CMR) data were collected for 22 patients. No statistical correlations were identified between p90RSK activation and any of the Echo and CMR parameters. DISCUSSION: Despite some setbacks due to the pandemic, we are near target accrual to this study. We still need to enlist 8 more lymphoma patients but have completed accrual to the thoracic cancer cohorts. We are actively working with the lymphoma department to fulfill the accrual goal of 30 evaluable patients across primary tumor diagnoses. Due to the COVID-19 delays in patient accrual, we are submitting for a no-cost extension and adjustment in timelines to complete the target patient enrollment and data collection.

	For a subset of patients, global longitudinal strain (GLS) declines were seen, whereas it is preserved in the majority of patients. Long-term follow-up with repeat scans will be needed to determine if the changes will continue to manifest or worsen. We will need additional follow-up on patients to determine if any of the imaging or blood biomarker changes correlate with clinical manifestation of cardiovascular disease as a result of radiation injury. Further analysis of cytokines and cardiac enzymes, as well as imaging data, will be integrated with preliminary results described here.
Bibliography Type:	Description: (Last Updated: 08/07/2023)
Articles in Peer-reviewed Journals	Kotla S, Zhang A, Imanishi M, Ko KA, Lin SH, Gi YJ, Moczygemba M, Isgandarova S, Schadler KL, Chung C, Milgrom SA, Banchs J, Yusuf SW, Amaya DN, Guo H, Thomas TN, Shen YH, Deswal A, Herrmann J, Kleinerman ES, Entman ML, Cooke JP, Schifitto G, Maggirwar SB, McBeath E, Gupte AA, Krishnan S, Patel ZS, Yoon Y, Burks JK, Fujiwara K, Brookes PS, Le NT, Hamilton DJ, Abe JI. "Nucleus-mitochondria positive feedback loop formed by ERK5 S496 phosphorylation-mediated poly (ADP-ribose) polymerase activation provokes persistent pro-inflammatory senescent phenotype and accelerates coronary atherosclerosis after chemo-radiation." Redox Biol. 2021 Nov;47:102132. http://dx.doi.org/10.1016/j.redox.2021.102132 ; PMID: 34619528; PMCID: PMC8502954 , Nov-2021