Fiscal Year:	FY 2021	**Task Last Updated:**	FY 07/15/2021
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:**	08/22/2022
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:	Zawaski, Janice	**Contact Phone:**	
Contact Email:	janice.zawaski@nasa.gov		
Flight Program:			
Flight Assignment:	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. Junichi 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, Junichi 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:	RESULTS: To date, 24 patients have been identified and enrolled in protocol PA16-0971 with at least one baseline imaging. However, only 22 patients have been considered evaluable if more than one imaging has been acquired. Due to COVID-19 pandemic in 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. Comparing the cardiovascular parameters using the 3 different devices (cardiac MRI (CMR), cardiac Echo, and Fully Integrate Toilet (FIT) seat)), we compared the robustness of data collection on these three different modalities. We found that the left ventricular end diastolic volume and the left ventricular end systolic volume correlate comparing CMR and Echocardiogram. Furthermore, comparing FIT with CMR and Echo measurements, we find the strongest correlation between FIT and Echo measurements in stroke volume (SV) measurements but not with CMR. Serum Biomarkers: Blood samples collected before, during, and at the end of RT were processed for 17 patients. The levels after H2O2 stimulation of p90RSK activity as a percentage of CD14+ PBMCs from pre-RT, mid-radiation treatment (2-3 weeks), and end of RT (3 months) were determined using the ratio between phosphorylated p90RSK and total p90RSK, detected by flow cytometry. 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 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 CMR data were collected for 22 patients. While in the short follow up for these patients, we have not had a clinically actionable cardiovascular event, some patients had Global Longitudinal Strain (GLS) declines on CMR of 2-5% range at the end of radiation or at first follow up. However, what was especially significant is the number of dysfunctional GLS segments >10 in a significant proportion of patients. On Chi-square test, these changes were not

	significantly correlated with the P90RSK changes seen. What we found significantly positively correlated was between activated P90RSK levels in the peripheral blood cells and the left ventricular end diastolic volume measured on CMR at the end of treatment (R2=0.376, p=0.045). DISCUSSION: Despite some setbacks due to the pandemic, we are near accrual to this study. We still need to enlist 8 more lymphoma patients but have completed accrual to the thoracic cancer cohorts. We are currently working with the lymphoma department to determine if this is something they would accrue to or that we will expand the patients to incorporate additional thoracic cancer patients in order to fulfill the accrual goal of 30 evaluable patients. For a subset of patients, 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 date will be integrated with preliminary results described here.
Bibliography Type:	Description: (Last Updated: 08/07/2023)
Abstracts for Journals and Proceedings	Kotla S, Abe J, Lin S, Milgrom S, Imanishi M, Ko K, Gi Y, Fujiwara K, Le N, Dabaja B, Slack Tidwell R, Chung C. "Monocyte and macrophage priming and cardiovascular injury from radiation exposure: Potential role of PARP activation." 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