Fiscal Year:	FY 2021	**Task Last Updated:**	FY 04/01/2021
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome		
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:	david.goukassian@mssm.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	617-480-3890
Organization Name:	Icahn School of Medicine at Mount Sinai		
PI Address 1:	Zena & Michael A. Weiner Cardiovascular Institute		
PI Address 2:	One Gustave L. Levy Place, Box 1030		
PI Web Page:			
City:	New York	**State:**	NY
Zip Code:	10029	**Congressional District:**	12
Comments:	NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018.		
Project Type:	Ground	**Solicitation / Funding Source:**	2016-2017 HERO NNJ16ZSA001N-SRHHC. Appendix E: Space Radiobiology and Human Health Countermeasures Topics
Start Date:	04/10/2019	**End Date:**	04/09/2023
No. of Post Docs:	2	**No. of PhD Degrees:**	0
No. of PhD Candidates:	2	**No. of Master' Degrees:**	1
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Zawaski, Janice	**Contact Phone:**	
Contact Email:	janice.zawaski@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome," grant 80NSSC18K0921, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University. (Ed., 2/10/2020)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
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Performance Goal No.:			
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Task Description:	Ed. note 2/10/2020: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Sex on the Outcome," grant 80NSSC18K0921 with the same Principal Investigator Dr. David Goukassian, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University. During the future Moon, near Earth asteroids, and Mars missions, astronauts will be exposed to higher total doses of space irradiation (IR) (~0.4-0.5 Gy) from galactic cosmic rays (GCR). Most of what we know about harmful effects of IR on cardiovascular (CV) system is from epidemiological studies of long-term survivors of cancer radiotherapy (RT). A recent study of 2,168 women who underwent RT for breast cancer has shown that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no apparent lower or upper threshold. In this study, it was determined that average of the mean doses to the whole heart was 4.9 Gy with the range of 0.03 - 27.72 Gy. Furthermore, metabolomics studies, in patients undergoing hematopoietic stem cell (HSC) transplantation as part of cancer treatment (1.25 Gy total-body irradiated), identified seven urine-based biomarkers with distinct differences between pre- and post-exposure samples. The levels of these markers were found to be sex-dependent suggesting that separate biomarker signatures may exist for males and females. Hypotheses: Our central hypothesis is that low-dose proton and HZE (high energy) particle IR-induced biological responses are long-lasting, IR type- and dose-dependent and may augment excess relative risk (ERR) estimates for the development of CV diseases during and after long-duration space missions. In addition, we hypothesize that sex differences could further modify radio-biologically effective (RBE) IR thresholds for CV risk estimates. Gene expression and epigenetic modifications in protein and microRNA (miRNA) in exosomes from the blood (e.g., plasma/serum) may be altered before the onset of the cardiac symptoms, which could be used as potential biomarkers to predict the CV disease risks. We will test our hypotheses with the following specific aims: AIM 1. Determine the longitudinal effect of IR type, dose, and sex on cardiovascular physiology in wild type mice and ApoE null mice after full-body 5-ion simplified mixed field and gamma radiation. AIM 2. Determine space-type IR mediated modulations in exosomal cargo in the blood, and determine whether these changes are associated with alterations in the heart function, structure, and vasculature before manifestation of clinical symptoms. AIM 3. Utilize known and newly identified bio-markers in the blood to develop human-relevant point-of-care tests (POCT) for predicting and monitoring possible CV alterations before and during the space flights. We anticipate that the results of our proposed work may be beneficial for human space exploration and could (1) Determine single, low-dose 1H, 56Fe, and mixed field dose-responses, radio-biologically effective IR thresholds in the heart and cardiac vasculature, and whether sex differences could modify radio-biologically effective IR thresholds for CV risk estimates; 2) Determine whether space radiation leads to modifications in the circulating exosomal cargo contents and whether IR-induced exosomal cargo modulations are reflective of subclinical changes in the cells and organs of origin; 3) Ascertain if modulations of exosomal cargo may be representative of chronic oxidative stress and inflammation and could serve as early bio-markers of IR-induced CV disease initiation and progression; 4) Integrate physiological CV endpoint data sets with gene expression and epigenetic data to identify bio-markers in bio-fluids that could be used for prediction of asymptomatic CV disease in the setting of space IR, which will include known early and intermediate bio-markers of cardiac damage, inflammation, and oxidative stress, as well as currently unknown novel radiation-associated cardiac bio-markers.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	We anticipate that the results of our work could be beneficial for human space exploration as well as for the Earth-based applications on several levels -- (1) determine whether low dose space-type and terrestrial IR may present an increased risks for CV disease development during and after prolonged space missions, as well as after conventional and particle cancer radiotherapy; (2) determine the underlying molecular signaling of CV alterations; (3) identify bio-markers in the blood that could be used for prediction of asymptomatic CV disease, which will include known early and intermediate bio-markers of cardiac damage, as well as currently unknown novel cardiac biomarkers; (4) the identification of sub-clinical CV disease biomarkers that could be used for monitoring the effectiveness of mitigating factors for prevention and treatment of IR-induced CV diseases in space and in Earth-bound civilian population, in general.
	In late September 2018, we irradiated at the NASA Space Radiation Laboratory (NSRL) and the Brookhaven National Laboratory (BNL) gamma facility 660 ApoE null male mice and 480 C57Bl/6J male mice, first two cohorts of our longitudinal lifetime studies. In terms of selection of radiation parameters, we utilized the following doses, energies, and ions, as recommended by Radiation Biology Element Management: (i) Gamma IR - 100, 200, and 400 cGy, using ApoE null MALE mice for all time points indicated above. (ii) 5-Ion Simplified Mixed field (simGCRsim) IR – 50, 100, and 150 cGy, adjusted to 500 MeV/n, using ApoE null MALE mice for all time points indicated above. (iii) Gamma IR – 100 and 200 cGy, using WT-C57BL/6J MALE mice for all time points indicated in section above. (iv) 5-Ion Simplified Mixed field (simGCRsim) IR – 50 and 100 cGy, adjusted to 500 MeV/n, using WT-C57BL/6J MALE mice for all time points indicated above. At the time of this report, we have collected functional cardiac echocardiography data as well as various tissues and blood from animals at all five designated time points (14 days and 28 days post IR as well as 12-, 16-, and 22- months post IR). Our updated findings are as follows: With regards to left ventricular (LV) cardiac function: Cardiac function was assessed non-invasively in all control and irradiated ApoE null and C57Bl/6J mice by transthoracic echocardiography (ECHO) at baseline (before IR) as well as at acute time points post IR (14 and 28 days) and chronic time points (12-, 16- and 22-months post IR). To summarize our findings: A single full-body IR at doses of 100-400 cGy for gamma- IR and 50-150 cGy for simGCRsim-IR decreases the global systolic function of the heart in both ApoE null and WT mice at 14 and 28 days after exposure. Histological analyses of H&E stained slides at 28 days after radiation showed – (i) multifocal myofiber disarray with mildly increased variation

Task Progress:	in myofiber diameter; (ii) swollen myocytes; (iii) mild to moderate sarcoplasmic swelling; (iv) minimal multifocal mineralization of few myofibers within papillary muscles. This suggests inducible alterations in cardiac tissues morphology are detectible early on in response to altered LV function. Our lifetime study reveals that at these doses, cardiac function is significantly affected at 22 months post-IR in both mouse genotypes. Interestingly, WT mice have an intermediate time point (12 months) where impairment in LV function is observed. Our data suggests, WT IR-mice may be exhibiting more diastolic dysfunction and compensation due to pressure overload, while our ApoE null mice LV functional impairment appears more consistent with a volume overloaded system as noted by increased LV dimensions and size. At 22 months, ApoE null gamma-IR mice exhibit significant systolic dysfunction; however, this does not exclude possibility of diastolic dysfunction in remining IR groups and mouse genotypes. Cardiac tissue responses, morphology, structure, and underlying molecular mechanisms are being analyzed for later time points. Overall, these findings do not exclude the possibility of increased acute or degenerative CV disease risks at lower doses of space-type IR and/or when combined with other space travel-associated stressors, such as microgravity. Vascular plaque burden: We assessed the effects of gamma- and simGCRsim-IR on vascular plaque burden along with fibrosis development and progression in ApoE null mice. We collected the aortic root with ascending aorta, and aortic arch with carotids and descending aorta from ApoE null and WT mice at 14 and 28 days, as well as 12-, 16-, and 22-months post-IR. ApoE null en face aortas were stained with Oil-Red-O to quantify plaque burden. To summarize our findings, the highest plaque burden is observed in non-IR western diet (WD)-fed mice at 12 months compared to remaining treatment groups. However, there was an ~1.5-fold increase plaque burden in the descending aorta and full aorta from 16 to 22 months in 50 cGy simGCRsim-IR mice. Progression in full aortic and descending aorta plaque burden is also seen in gamma-IR mice from 12 to 22 months, with a 2-fold increase in vascular plaque over a 10-month period. These findings further suggest that simGCRsim- and gamma-IR may accelerate plaque progression and suggest simGCRsim-IR may be doing so at a higher rate compared to gamma-IR. Our data suggests there is potential IR induced acceleration in plaque progression between the 16- and 22-month time points that is possibly more pronounced with simGCRsim-IR, and that could make the long-term effects of IR comparable to that of a WD. Further work is underway for quantification of fibrosis in both the aorta as well as the aortic root for all treatment groups. Further analyses including in WT mice is underway. Right ventricular (RV) function: We hypothesize that space-type IR may potentiate pulmonary hypertension and lung fibrosis, therefore inducing vascular remodeling and affecting the right ventricular (RV) morphology and function. Thus, we assessed the effects of gamma-IR (100, 200 cGy) and simGCRsim-IR (50, 100, 150 cGy) on the structure and the function of the heart and lungs over a 22-month post-IR follow up. Our results showed that full-body gamma- and simGCRsim-IR potentiates the mRNA expression of proliferation, oxidative stress, and inflammation gene markers, as well as vascular remodeling and fibrosis in lung tissue as early as 28 days post IR. Compared to controls, morphometric measurements revealed an increase of the intima-media thickness of the distal pulmonary arteries after both types of IR. In addition, there was a significant increase in perivascular inflammatory infiltration in the lung tissue after simGCGsim radiation with a substantial perivascular fibrosis of pulmonary arteries. Concomitantly, compared to controls, a significant increase in right ventricular systolic pressure (RVSP) after exposure to gamma-IR 200 cGy or simGCRsim 100 cGy was observed at 12-month post IR exposure. Echo analyses at 22-months revealed significant increases in RV internal diameter (RVIDs) in ApoE null mice after all doses of simGCRsim, whereas WT mice revealed 2-fold decreases in RV diameter at mid-level after all doses and types of radiation. However, the structural and functional changes such as increases in pulmonary artery diameter and pulmonary valve maximum velocity were detected only in mice exposed to 50 cGy of simGCRsim and 200 cGy of gamma-IR. Collectively, these findings indicate that both types of radiation may have deleterious effects on the RV and lung structure and function that may lead to the development of pulmonary arterial hypertension.
Bibliography Type:	Description: (Last Updated: 07/08/2025)
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