

Fiscal Year:	FY 2022	Task Last Updated:	FY 03/07/2022
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender 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:	Elgart, Robin	Contact Phone:	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender 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):			
Grant/Contract No.:	80NSSC19K1079		
Performance Goal No.:			
Performance Goal Text:			

	<p>Ed. note 2/10/2020: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender 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.</p> <p>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 gender-dependent suggesting that separate biomarker signatures may exist for males and females.</p> <p>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 cardiovascular diseases (CVDs) during and after long-duration space missions. In addition, we hypothesize that gender 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 CVD risks. We will test our hypotheses with the following specific aims:</p> <p>AIM 1. Determine the longitudinal effect of IR type, dose, and gender on cardiovascular physiology in wild type mice and ApoE null mice after full-body 5-ion simplified mixed field and gamma radiation.</p> <p>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 the manifestation of clinical symptoms.</p> <p>AIM 3. Utilize known and newly identified biomarkers in the blood to develop human-relevant point-of-care tests (POCT) for predicting and monitoring possible CV alterations before and during space flights.</p> <p>We anticipate that the results of our proposed work may be beneficial for human space exploration and could (1) Determine single whole body mixed field dose-response, radio-biologically effective IR thresholds in the heart and cardiac vasculature, and whether gender 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 biomarkers of IR-induced CVD initiation and progression; 4) Integrate physiological CV endpoint data sets with gene expression and epigenetic data to identify biomarkers in bio-fluids that could be used for prediction of asymptomatic CVD in the setting of space IR, which will include known early and intermediate biomarkers of cardiac damage, inflammation, and oxidative stress, as well as currently unknown novel radiation-associated cardiac biomarkers.</p>
Task Description:	
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>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 risk for CVD 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 biomarkers in the blood that could be used for prediction of asymptomatic CV disease, which will include known early and intermediate biomarkers 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 CVDs in space and in Earth-bound civilian population, in general.</p>
	<p>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, the first two cohorts of our longitudinal lifetime studies. We completed and performed cardiac function analyses and harvested tissues and blood for 5 harvesting time points (14, 28, 365, 440, and 660 days post-irradiation). In terms of selection of radiation parameters, we utilized the following doses, energies, and ions, as recommended by Space Radiation Element Management: (i) Gamma IR - 1, 2, and 4 Gy, using ApoE null MALE mice for all time points indicated above. (ii) 5-Ion Simplified Mixed field IR - 0.5, 1.0 and 1.5 Gy, adjusted to 500 MeV/n, using ApoE null MALE mice for all time points indicated above. (iii) Gamma IR - 1, 2 Gy, using WT-C57Bl/6J MALE mice for all time points indicated in section above. (iv) 5-Ion Simplified Mixed field IR - 0.5, 1.0 Gy, adjusted to 500 MeV/n, using WT-C57Bl/6J MALE mice for all time points indicated above.</p> <p>Lifetime tumor burden As part of our study to assess the effects of space radiation on cardiovascular disease (CVD) risks, male mice were systematically examined for tumor development during scheduled tissue collections over 660 days after initial radiation (IR) exposure. We report:</p> <ul style="list-style-type: none"> • The incidence of tumors is higher in wild type (WT) compared to ApoE null male mice after the same doses of gamma- and simGCRsim-IR suggesting underlying genotypic variance may attenuate pathways involved in tumorigenesis; • The highest number of tumors during the lifetime of WT male mice was detected in the no-IR, Western diet-fed (WD-fed) group, suggesting the role of high fat diet in the development of internal organ tumors, especially in the liver; • In WT male mice, the incidence of IR-induced internal organ tumors was higher in 100 cGy gamma-IR versus 50 cGy simGCRsim-IR, suggesting higher carcinogenic potential of gamma-IR at these doses; • In WT male mice, the liver is the most affected organ by tumor growth, followed by the spleen, and lung;

	<ul style="list-style-type: none"> • There was a higher incidence of hepatic and splenic tumors in mice fed with WD or exposed to both types of IR in WT mice approaching end of life; • In ApoE null male mice, the incidence of IR-induced tumors was higher in 50 cGy simGCRsim-IR mice with a higher prevalence of lung tumors. <p>In October 2020, we have irradiated at the NSL and the BNL gamma facility an additional 160 ApoE null female mice and 300 C57BL/6J female mice. This longitudinal life-time study is designed to have 5 harvesting time points (28, 180, 365, 440, and 660 days). We have already performed cardiac function analyses and harvested tissues for 4 of our harvesting time points (28, 180, 365, and 440 days). The final collecting time point is scheduled for July 2022. In terms of selection of radiation parameters, we utilized the following doses, energies, and ions, as recommended by Space Radiation Element Management:</p> <p>(i) Gamma IR – 1 Gy, using ApoE null and WT FEMALE mice for all time points indicated above. (ii) 5-Ion Simplified Mixed field IR - 0.5 Gy, adjusted to 500 MeV/n, using ApoE null FEMALE mice. (iii) 5-Ion Simplified Mixed field IR - 0.25, 0.50 cGy adjusted to 500 MeV/n, using WT-C57BL/6J FEMALE mice for all time points indicated above.</p> <p>Left ventricular (LV) cardiac response to IR.</p> <p>Cardiac function was assessed non-invasively in all control and irradiated ApoE null and C57BL/6J female mice by transthoracic echocardiography at 28, 180, and 365 days post-IR. Each mouse is microchipped and followed longitudinally.</p> <p>To briefly summarize our male cohort echocardiography findings:</p> <ul style="list-style-type: none"> • A single full-body IR at doses of 100-200 cGy for gamma- IR and 50-100 cGy for simGCRsim-IR decreases global LV systolic function in WT male mice at 14, 28, and 365 days post-IR. • At 660 days post-IR, 50 cGy simGCRsim-IR WT male mice exhibited increased diastolic stiffness paired with alterations in LV size and mass, suggesting these mice may be exhibiting additional diastolic dysfunction and compensation as a result of pressure overload. • In ApoE null male mice, global LV systolic function is impaired as early as 14 and 28 days post-IR in both simGCRsim (100, 200, 400 cGy) and gamma- IR (100, 200 cGy) mice. Interestingly, there is no intermediate time point (365, 440 days) where LV dysfunction is noted. • By 660 days post-IR, gamma-IR ApoE null male mice exhibit significant systolic dysfunction with reduction in Left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), and increases in stroke volume (SV), LV mass, and LV dimensions suggesting compensation for likely volume overload. No significant changes in LV function were noted in simGCRsim-IR ApoE null male mice at 660 days. • No clear dose-response was observed in these studies. <p>In our female longitudinal cohort:</p> <ul style="list-style-type: none"> • A single full-body IR at doses of 100 cGy for gamma-IR and 25 or 50 cGy for simGCRsim-IR decreases the global systolic function of the heart in both ApoE null and WT female mice at 28 days post-IR. • At later time points (180, 365 days), no significant alterations in global LV systolic function are noted; however, in WT female mice, there is evidence of alterations in LV structure suggesting ongoing remodeling. • Further work is underway to collect additional data to assess long-term degenerative effects of IR (440, 660 days) in female WT and ApoE null mice. Analysis of additional echocardiography parameters to assess LV remodeling are underway. <p>These findings do not exclude the possibility of increased acute or degenerative CVD risks at lower doses of space-type IR and/or when combined with other space travel-associated stressors, such as microgravity.</p>
Bibliography Type:	Description: (Last Updated: 03/06/2024)
Abstracts for Journals and Proceedings	<p>Brojakowska A, Fish K, Khlgatian M, Grano C, Bissierier M, Zhang S, Saffran N, Chepurko V, Chepurko E, Gillespie V, Dai Y, Hadri L, Kishore R, Goukassian D. "Longitudinal evaluation of cardiac function and structure in C57BL/6J mice after gamma and space-type radiation exposure." 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022.</p> <p>Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022, Abstract #1133-000167. , Feb-2022</p>
Abstracts for Journals and Proceedings	<p>Brojakowska A, Bissierier M, Elmas A, Khlgatian M, Zhang S, Gillespie V, Dai Y, Hadri L, Goukassian D. "Lifetime risk of tumor development in C56B1/6J mice fed with Western diet or exposed to a single full body gamma or simGCRsim radiation." 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022.</p> <p>Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022, Abstract #1133-000425. , Feb-2022</p>
Abstracts for Journals and Proceedings	<p>Jackson C, Brojakowska A, Blattnig S, Khlgatian M, Grano C, Fish K, Chepurko V, Chepurko E, Kishore R, Goukassian D. "The comparative effect of gamma and simplified GCR simulation irradiation on cardiac response in ApoE null mice." NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022.</p> <p>Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022, Abstract #1133-000142. , Feb-2022</p>
Articles in Peer-reviewed Journals	<p>Bissierier M, Saffran N, Brojakowska A, Sebastian A, Evans AC, Coleman MA, Walsh K, Mills PJ, Garikipati VNS, Arakelyan A, Hadri L, Goukassian DA. "Emerging role of exosomal long non-coding RNAs in spaceflight-associated risks in astronauts." Front Genet. 2022 Jan 17;12:812188. https://doi.org/10.3389/fgene.2021.812188 , Jan-2022</p>