

Fiscal Year:	FY 2020	Task Last Updated:	FY 02/21/2020
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		
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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:	0	No. of Master' Degrees:	0
No. of Master's Candidates:	1	No. of Bachelor's Degrees:	0
No. of Bachelor's Candidates:	0	Monitoring Center:	NASA JSC
Contact Monitor:	Simonsen, Lisa	Contact Phone:	
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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):			
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 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.</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 sex-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 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:</p> <p>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.</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 manifestation of clinical symptoms.</p> <p>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.</p> <p>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.</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 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.</p> <p>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.</p> <p>At the time of this report preparation we collected functional cardiovascular data and various tissues for 4 time points – 14, 28 days and 12, 16 months. Within this time points we have established five sub-projects and each is reported here separately as sub-project 1-5. The utilized radiation ions, doses, and energies used in these studies as recommended by Radiation Biology Element of the Human Research Program (HRP) and depicted below:</p> <p>(i) Gamma IR - 1, 2, and 4 Gy, using ApoE null MALE mice.</p> <p>(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.</p> <p>(iii) Gamma IR - 1 and 2, using WT-C57BL/6J MALE.</p> <p>(iv) 5-Ion Simplified Mixed field IR - 0.5 and 1.0 Gy, adjusted to 500 MeV/n, using WT-C57BL/6J MALE mice.</p> <p>SUB-PROJECT 1. Title - "FULL BODY GAMMA AND 5-ION SIMPLIFIED MIXED ION RADIATION AFFECT CARDIAC FUNCTION AND STRUCTURE IN APOE NULL AND C57BL/6 MICE"</p> <p>Preliminary Summary: Gamma- and 5-ISMF full body radiation, at doses 100-400 cGy for gamma and 50-150 cGy for 5-ISMF-IR, decrease global systolic function of the heart in both ApoE null and C57BL/6 mice at 14 and 28 days after exposure. Presence of global systolic dysfunction already by 14 and 28 days post-IR determined by echocardiography (ECHO) and identification of the first detectable changes in the heart tissue only by day 28 after IR, may indicate that alterations in cardiac contractile function could be detected in advance of morphological changes in the heart tissue, suggesting that echocardiography may be one of the early tests to identify CV disease risk development. Compared to control non-irradiated mice, the left ventricular global systolic function continued to deteriorate at 12 and 16 month after</p>

Task Progress:	<p>exposure, with revealing detectable by echocardiography structural alteration in LV septal wall thickness, as well as other functional ECHO parameters. Additional studies are ongoing to confirm these results and further characterize the functional and histological alterations in cardiac structure and function.</p> <p>SUB-PROJECT 2. Title - "EFFECTS OF FULL BODY SPACE RADIATION ON RIGHT VENTRICULAR CARDIAC FUNCTION AND DEVELOPMENT OF PULMONARY HYPERTENSION"</p> <p>Preliminary Summary: At this time, our data suggested that both gamma and 5-ion simplified mix field radiation induce lung damage as characterized by vascular remodeling and increased perivascular fibrosis, proliferation, oxidative stress, and inflammation markers in the lung tissue 28 days and 1 year post radiation. Our results suggested that gamma and 5-ion simplified mix field ion radiation may potentiate fibrosis that could results in pulmonary hypertension.</p> <p>SUB-PROJECT 3. Title - "FULL BODY GAMMA AND 5-ION SIMPLIFIED MIXED ION RADIATION AFFECT VASCULAR PLAQUE BURDEN IN APOE NULL MICE"</p> <p>Preliminary Summary: SimGCRsim full body radiation, at a dose of 100cGy in ApoE null mice increase plaque burden at 1 year after exposure. The absence of aortic plaque burden was documented at 14 and 28 days post-IR determined by Oil-Red staining, imaging, and image analyses. Identification of the major detectable changes in the aortas and carotid arteries that was documented at one year after IR may accelerate atherosclerotic plaque development and/or progression when combined with natural aging processes. Further analyses including in vascular cells function/dysfunction in aorta and carotids in Wild Type mice, as well as the extended longitudinal studies in ApoE null mice are ongoing.</p> <p>SUB-PROJECT 4. Title - "PERIPHERAL BLOOD DERIVED EXOSOMAL miRNA AS BIOMARKERS FOR SPACE RADIATION-ASSOCIATED CARDIOVASCULAR DISEASE DEVELOPMENT"</p> <p>Preliminary Summary: Results of our studies so far indicate that ionizing radiation alters the miRNA content in peripheral blood derived exosomes of gamma and 5-ISMF full body irradiated mice (both, 100 cGy dose), which can be used as a source of potential biomarkers for cardiac tissue damage. Top five miRNAs were represented by miR223-3p, miR503-3p, miR149-5p (upregulated more than 2-fold after both IRs), and miR1964-3p, miR3068-3p (downregulated more than 2-fold after both IRs). The bioinformatics analyses of miRNA-223-3p and miR-503-3p target mRNAs shared common genes in vascular, cardiac, and metabolic regulatory pathways, e.g., BRINP3, LRP8, SOX11, MEF2C, IL6ST, IGF1R and NTSC1, ADAMTSL1, ABCB1, CCL2, NKAIN2, respectively. Therefore, with further functional and structural validation, exosomal miRNAs could prove to be promising candidate biomarkers for identification and validation of tissue specific damage/pathology for space-type radiation-induced cardiovascular diseases.</p> <p>SUB-PROJECT 5. Title - "SPACE RADIATION AND HIGH LIPID DIET-ASSOCIATED BRAIN DENDRITIC CELL ACTIVATION: IMPLICATIONS FOR NEUROLOGICAL DISEASE DEVELOPMENT"</p> <p>Preliminary Summary: Gross examination of brains from irradiated Apo-E mice appears to suggest that 5-Ion Simplified Mix Field-IR (5-ISMF IR) results in increased number of melanocyte-like dendritic cells in western diet-fed and 5-ISMF IR exposed mice meninges. We also detected elevated levels of cells appearing in several pyramidal and granular layers of the cerebral cortex in the 100 cGy 5-ISMF irradiated animals. Congo Red staining for amyloid staining was negative, suggesting that there were no hallmark AD lesions present. Further follow up is needed to confirm these results and further characterize the progression of lesions identified.</p>
Bibliography Type:	Description: (Last Updated: 04/04/2025)
Abstracts for Journals and Proceedings	<p>Fish K, Khlgatian MK, Bisserier M, Zhang S, Hadri L, Hajjar R, Kishore R, Goukassian DA. "Full body gamma and 5-ion simplified mixed ion radiation affect vascular plaque burden in apoe null mice." Presented at the 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020.</p> <p>Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020</p>
Abstracts for Journals and Proceedings	<p>Bisserier M, Zhang S, Khlgatian MK, Fish K, Goukassian DA, Hadri L. "Effects of full body space radiation on right ventricular cardiac function and development of pulmonary hypertension." Presented at the 2020 NASA Human Research Program Investigators Workshop, Galveston, TX, January 27-30, 2020</p> <p>Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020</p>
Abstracts for Journals and Proceedings	<p>Khlgatian MK, Bisserier M, Zhang S, Chepurko V, Chepurko V, Gillespie V, Dai Y, Fish K, Hadri L, Hajjar R, Kishore R, Goukassian DA. "Full body gamma and 5-ion simplified mixed ion radiation affect cardiac function and structure in apoe null and c57bl/6 mice." Presented at the 2020 NASA Human Research Program Investigators Workshop, Galveston, TX, January 27-30, 2020</p> <p>Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020</p>
Abstracts for Journals and Proceedings	<p>Fish K, Bisserier M, Khlgatian MK, Adamiak M, Mathiyalagan P, Hajjar R, Kishore R, Sahoo S, Goukassian DA. "Peripheral blood derived exosomal miRNA as biomarkers for space radiation-associated cardiovascular disease development." Presented at the 2020 NASA Human Research Program Investigators Workshop, Galveston, TX, January 27- 30, 2020</p> <p>Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020</p>
Abstracts for Journals and Proceedings	<p>Fish K, Bisserier MM, Zhang S, Hadri H, Khlgatian MK, Goukassian DA. "Space radiation and high lipid diet-associated brain dendritic cell activation: implications for neurological disease development." Presented at the 2020 NASA Human Research Program Investigators Workshop, Galveston, TX, January 27-30, 2020</p> <p>Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020</p>