Fiscal Year:	FY 2018	**Task Last Updated:**	FY 05/09/2018
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Degenerative Cardiovascular Disease Risks Due to Single HZE or Mixed Ion Radiation		
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-Crew Health (FLAGSHIP, OMNIBUS). Appendix A-Omnibus, Appendix B-Flagship
Start Date:	06/28/2017	**End Date:**	04/09/2020
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018. Grant continues at Icahn School of Medicine at Mount Sinai through 4/9/2020 with new grant number 80NSSC19K1078 (Ed., 3/30/2020)		
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Performance Goal No.:			
Performance Goal Text:			

Task Description:	During the future Moon and deep space missions to Mars, astronauts will be exposed to higher total doses of ionizing space radiation (IR, ~0.4-0.5 Gy) from galactic cosmic rays (GCR), especially during Mars missions that are currently estimated to be 30 to 36 months. Due to GCR, each cell in an astronaut's body will be traversed by a proton (1H) every week, helium (2He) nuclei every few weeks, and high charge and energy (HZE) nuclei (e.g., 6C, 8O, 14Si, 22Ti, 56Fe) every few months. These frequencies and qualities of IR exposures could have significant effects on cardiovascular (CV) health of astronauts during and after exploration-type space missions. In spite of healthy worker factor (unsurpassed training and fitness of astronauts) such factors are of extreme importance as majority of experienced astronauts are middle-aged and at higher risk for developing serious CV complications. We hypothesize that low-dose proton and HZE particle IR-induced biological responses are long-lasting, IR type-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 different sequence of proton vs. HZE and mix beam radiation regimens could further modify radio-biologically effective (RBE) IR thresholds for CV risk estimates. To determine qualitative differences and quantify RBEs for biological damage induced by proton and HZE particles for various HZE ions and mix beam IR regimens and how this may influence late degenerative CV disease risks, we will use our own archived heart samples from fractionated proton and single iron IR used in various sequences. In addition, we plan to use the archived samples from experiments conducted by Drs. Eleanor Blakely and Polly Chang where they used CB6F1/Hsd female mice of 100-120 days at the time of initial exposure and tissues were harvested 16 months after IR. These samples fit very well with our own low dose proton and iron single and fractionated studies, as ions and energies used in these studies are complementary to our studies. Additionally, these samples provide an experimental synergy and continuity to our archived samples for testing the effect of low dose gamma and various HZE particle IR of different doses, energies, and sequences on IR responses in the heart. We anticipate that the results of our work could be beneficial for human space exploration on several levels: (1) determine whether low dose space-type IR may present an increased risks for late degenerative CV disease development including, but not limited to, fibrosis, atherosclerosis, and vascular changes; (2) determine whether there may be low dose thresholds for radiation-induced changes in the heart tissue; (3) lay a foundation for identification of common bio-markers for different species and energies of space-type IR that could be used for prediction of asymptomatic CV disease in the setting of space IR; (4) provide an insight, on the cardiac tissue level, of molecular targets/pathways for development of mitigating factor and biological countermeasures.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The results of these studies could be beneficial for human space exploration on several levels: Research Impact: (1) determine whether low dose space IR may present an increased risk for CV disease development; (2) elucidate whether manifestation of sub-clinical or environmentally induced CV diseases due to space radiation could be predicted; (3) elucidate underlying molecular mechanisms of CV alterations; (4) lay foundation for identification of predictive biomarkers to monitor CV risks and sub-clinical CV pathologies due to low dose single and mix ion fractionated HZE particle radiation regimens; Earth and Space benefits: (5) provide mechanistic insights for molecular targets/pathways for development of mitigating factors to prevent CV morbidity in astronauts during and after exploration type space missions and in civilian population after treatment with conventional and particle cancer radiotherapy.
	Objectives: in archived snap-frozen heart samples from experiments conducted by Drs. Eleanor Blakely and Polly Chang using CB6F1 female mice we sought to determine long-term effects on the gene expression in the whole heart as a function of IR type and dose. Methodology: We used archived samples of CB6F1 female mice that were 100-120 days old at the time of initial exposure and were irradiated with low dose of gamma-137Cs (160 cGy, 0.662 MeV), 14Si (32 cGy, 260 MeV/n), and 22Ti (two doses of 13 cGy, and 26 cGy, 1,000 MeV/n, both doses). Mice were sacrificed 16 months after a single dose of a full body radiation with the corresponding ions and doses above and various tissues included hearts were harvested 16 months after IR. Note, availability of gamma-IR samples would allow quantification of RBEs for HZE ions at various doses. Hypothesis: Different HZE particles may exhibit various radio-biologically effects and thresholds for CV surrogate endpoints at low doses and are IR-type and dose-dependent. Trascriptional Microarray Studies. Three biological samples/group were examined. Total RNA was isolated and quality was checked using a BioAnalyzer. Linear amplification of mRNA was performed using Whole-Transcript(TM) RNA amplification kits and for hybridizations Affymetrix array formats was used. Array hybridization and processing for statistical analysis was carried out as previously described in our published work. In this set we used a cut-off change of 2-fold up- or down-regulated gene expression compared to Non-IR control samples. Functional and network analysis was performed through the use of IPA core analysis software (Ingenuity® Systems, https://) and the Genomatix (https://) suite of analysis tools. Summary of Findings: Data analyses revealed that even after 16 months of a single dose of full body low dose radiation there were substantial changes in the gene expression (2 and higher-fold) after all irradiation types and dose. The main findings are presented below: 1. Compared to control samples, there were two distinct sets of gene – one was downregulated (18 genes) and the other set was upregulated (23 genes) 16 months after initial IR; 2. The highest number (246 genes) of differentially expressed genes (2-fold and higher) was observed after 160 cGy of GAMMA-irradiation, followed by 14Si, 260 MeV/n (76 genes), then 22Ti 13cGy 1,000 MeV/n (40 genes) and 22Ti 26 cGy 1,000 MeV/n (40 genes); 3. There were two genes that were common for all four radiation types and the expression of these two genes was changed in the same direction when compared to controls - Protein Phosphatase 1 Regulatory Subunit 3c (Ppp1r3c) was down-regulated in IR types, and Alcohol Dehydrogenase 1 (Adh 1) was upregulated in all IR types when compared to

Task Progress:	controls; 4. The genes expression changes in all four irradiation types predict various degrees of cardiovascular disease and cardiac function changes in three major categories: i) Cardiac Function and Structure – fibrosis of the heart, mass of heart, morphology of heart ventricle, enlargement of papillary muscle, hypertrophy of ventricular septum, abnormal morphology of heart ventricle, restrictive cardiomyopathy, ischemic cardiomyopathy, systolic pressure; ii) Vascular Endothelial Cell Structure and Function – hyperpermeability of blood vessels, vasculogenesis, angiogenesis, morphogenesis of microvasculature endothelial cells, proliferation of endothelial cells, atherosclerosis, occlusion of artery, restenosis of femoral artery, susceptibility to coronary artery disease, kidney ischemia, abnormal morphology of lymph vessels, leakage of vasculature. iii) Vascular Smooth Muscle Cell Structure and Function – formation of neointima, function of vascular smooth muscle, proliferation of vascular smooth muscle cells, blood pressure, mean arterial pressure, stenosis of aorta; iv) Lipid metabolisms – severe hypertriglyceridemia, hyperlipidemia – ONLY after 14Si 32 cGy, 260 MeV/n radiation. 5. Analyses of upstream regulators of genes in our data set have predicted regulation of various extra- and intracellular molecules in different categories that were similar after all radiation types, such as: i) Upstream Cytokines – FAM3B, CTF1, TNF, TIMP1, TNFSF11, IL1b; ii) Upstream Transmembrane Receptors – TNFRSF8, AGER, CAV1, IL6R, PRLR, CHRNA3, NCR2; iii) Upstream g-protein coupled receptors – NPSR1, HRH3, GPER1, F2RL1, CALCR, CXCR4, ADRB3, ACKR3, PTGFR, KISSIR; iv) Upstream Ion Channels – TRMP8, TRPC1, KCNE3, CLCA2; v) Upstream Ligand-dependent Nuclear Receptors – ESRRG, NR2E1, PPARG, PPARD, RORA, NR1HR, PPARA, RARB, RORC; vi) Upstream translational regulator – AGO1, SAMD4A, EIF4G2, CELF1; vii) Upstream miRNAs – miR-17, miR-7, miR-30, miR21, miR-34a-5p, miR-26-5p. 6. Current work and future plans: i) we are currently in the process of validating by qPCR the gene expression data; ii) in the formalin-fixed paraffin embedded samples of corresponding heart tissue we will be testing Cardiac, Vascular Endothelial and Vascular Smooth Muscle cell structural changes predicted by bio-informatics analyses presented in the section 4 above; iii) in the snap-frozen heart tissue and OCT embedded heart tissue we will be testing/validating predicted upstream regulators/molecules in different categories presented in the section 5 above; iv) to determine whether there may be a lower bio-effective threshold for each of the radiation type/dose/energy as well as to quantify RBE for heavy ions we are planning to perform transcriptional profiling of the rest of low and very low doses for each ion in the next year of the funding.
Bibliography Type:	Description: (Last Updated: 03/06/2024)