Pl Name:       Goukassian, David A M.D., Ph.D.         Project Title:       Degenerative Cardiovascular Disease Risks Due to Single HZE or Miscaliation         Division Name:       Human Research         Program/Discipline:				
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Organization Name:       Icahn School of Medicine at Mount Sinai         PI Address 1:       Cena & Michael A. Weiner Cardiovascular Institute         PI Address 2:       One Gustave L. Levy Place, Box 1030         PI Web Page:       Image: State:         City:       New York       State:         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 NN162SA001N-Crew Health Source:         No of Post Docs:       1       None Special Source:         No of Post Docs:       1       None Special Source:         No of Bost Docs:       1       None Special Source:         No of Bost Docs:       1       None Species:         No of Bachelor's Candidates:       1       None Species:         No of Bachelor's Candidates:       Isso e Simonsen/Gauss gov         Flight Assignment:       Simonsen/Gauss gov         Flight Assignment:       NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018. Grant Goutset E Mount Sinai from Temple University in October 2018. Grant Goutset E Mount Sinai from Temple University in October 2018. Grant Goutset E Mount Sinai from Temple University in October 2018. Grant Goutset E Mount Sinai from Temple University in October 2018. G	PI Email:	david.goukassian@mssm.edu	Fax:	FY
Pi Address 1:       Zena & Michael A. Weiner Cardiovascular Institute         Pi Address 1:       Cena Gustave L. Levy Place, Box 1030         Pi Address 1:       One Gustave L. Levy Place, Box 1030         Pi Web Page:       Image: Compressional District:         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.       2016-2017 IEERO         Project Type:       Ground       Solicitation / Funding Source:       2016-2017 MERO Source:       2016-2017 MERO Source:         No. of Pathere:       0628/2017       End Date:       04/09/2020         No. of Post Docs:       1       No. of Pathere:       04/09/2020         No. of Master's Candidates:       1       No. of Master' Degrees:       No. of Bachelor's Degrees:         No. of Bachelor's Candidates:       Simosen, Lisa       Contact Monitoring Center:       NASA JSC         Contact Monitor:       Simosen, Lisa       Contact Phone:       Source:         Flight Assignment:       Simosen Alexa ot Mount Sinai from Temple University in October 2018, Grant Source:       Source:       Source:         Contact Monitor:       State: Instruce University in October 2018, Grant Source: <t< td=""><td>PI Organization Type:</td><td>UNIVERSITY</td><td>Phone:</td><td>617-480-3890</td></t<>	PI Organization Type:	UNIVERSITY	Phone:	617-480-3890
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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 experiments conducted by Drs. Eleanor Blakely and POIP 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 fir 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 synerg
Rationale for HRP Directed Researc	h:
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.
	<ul> <li>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.</li> <li>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.</li> <li>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.</li> <li>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</li> </ul>
	<ul> <li>was performed through the use of IPA core analysis software (Ingenuity® Systems, <a href="https://www.ingenuity.com" target="_blank">https://</a>) and the Genomatix (<a href="https://www.genomatix.de" target="_blank">https://</a>) and the Genomatix (<a href="https://www.genomatix.de" target="_blank">https://</a>) suite of analysis tools.</li> <li>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:</li> <li>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;</li> </ul>
	<ol> <li>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);</li> <li>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</li> </ol>

Bibliography Type:	Description: (Last Updated: 07/08/2025)
	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.
	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;
	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;
	i) we are currently in the process of validating by qPCR the gene expression data;
	6. Current work and future plans:
	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.
	molecules in different categories that were similar after all radiation types, such as:
	<ul> <li>iv) Lipid metabolisms – severe hypertriglyceridemia, hyperlipidemia – ONLY after 14Si 32 cGy, 260 MeV/n radiation.</li> <li>5. Analyses of upstream regulators of genes in our data set have predicted regulation of various extra- and intracellular</li> </ul>
	proliferation of vascular smooth muscle cells, blood pressure, mean arterial pressure, stenosis of aorta;
	iii) Vascular Smooth Muscle Cell Structure and Function – formation of neointima, function of vascular smooth muscle
	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.
	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;
ask Progress:	4. The genes expression changes in all four irradiation types predict various degrees of cardiovascular disease and cardiac function changes in three major categories:
	controls;