Fiscal Year:	FY 2016	**Task Last Updated:**	FY 06/10/2016
PI Name:	Boerma, Marjan Ph.D.		
Project Title:	Center for Research on Cardiac, Vascular, and Acute Effects of Space Radiation		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Radiation Effects Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **ARS**:Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (2) **Degen**:Risk Of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure (IRP Rev F)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	72205-7101	**Congressional District:**	2
Comments:			
Project Type:	GROUND	**Solicitation:**	2013 NSBRI-RFA-13-02 Center for Space Radiation Research (CSRR)
Start Date:	06/01/2014	**End Date:**	05/31/2017
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Mao, Xiao (Loma Linda University) Hauer-Jensen, Martin M.D., Ph.D. (University of Arkansas for Medical Sciences) Kodell, Ralph Ph.D. (University of Arkansas for Medical Sciences) Koturbash, Igor M.D., Ph.D. (University of Arkansas for Medical Sciences) Tackett, Alan Ph.D. (University of Arkansas for Medical Sciences) Nelson, Gregory Ph.D. (Loma Linda University)		
Grant/Contract No.:	NCC 9-58-RE03701		
Performance Goal No.:			
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Task Description:	The Center for Space Radiation Research (CSRR) consists of teams of investigators from the University of Arkansas for Medical Sciences (UAMS), Loma Linda University (LLU), the University of Arizona, and Georgetown University. The CSRR uses multiple animal models to characterize acute effects of protons at doses lower than addressed in previous animal studies, and experiments involve exposure of animals and cell cultures to protons and heavy ions to examine degenerative cardiovascular effects. The CSRR pursues the following Specific Aims: 1) Define acute effects of low-dose proton irradiation on the hematopoietic system, skin, heart, and retina; 2) Examine acute effects of low-dose protons in combination with modeled microgravity; 3) Evaluate acute effects of protons on the adaptive immune response; 4) Determine effects of heavy ion and proton irradiation on cardiac and vascular function and structure; 5) Identify acute and chronic biomarkers of cardiovascular dysfunction after particle irradiation; 6) Elucidate the role of metabolic and epigenetic changes in the cardiovascular response to radiation; 7) Determine effects of radiation dose and quality on endothelial cell functional phenotype; and 8) Test whether gamma-tocotrienol protects against acute and cardiovascular effects of particle irradiation. In the grant's second year, the following progress was made: Under Specific Aim 1, the LLU team has performed studies with male C57BL/6 mice exposed to solar particle event (SPE)-like protons (0.1 - 0.5 Gy) or Cobalt-60 gamma rays as a reference radiation and examined at 60 hours and 14 days after irradiation. Both protons and gamma-rays at doses of 0.25 and 0.5 Gy caused apoptosis in the outer plexiform layer, inner nuclear layer, and ganglion cell layer of the retina. A double staining with lectin indicated that some of the apoptotic cells were from endothelial origin. Femurs and tibiae were shipped to UAMS for the analysis of hematopoietic cell populations. Protons at 0.5 Gy increased levels of reactive oxygen species (ROS) in hematopoietic stem cells (HSCs), but did not affect numbers of hematopoietic progenitor cells (HPCs), Lin- Sca1- c-kit+ (LSK) cells, or HSCs. Gamma rays reduced the percentages of HPCs, LSK cells, and HSCs within bone marrow-derived cells in a dose dependent manner and significantly increased ROS levels in LSK cells and HSCs at a dose of 0.5 Gy. Under Specific Aim 2, the LLU team has started studies with male C57BL/6 mice exposed to hindlimb unloading for 5 days, then exposed to SPE-like protons (0.5 Gy), followed by 5 more days of hindlimb unloading. Mice are sacrificed 4 days after completion of hindlimb unloading, and skin, heart, and eye are collected for histological and molecular analysis. These studies with radiation in combination with hindlimb unloading are ongoing. Under Specific Aims 4 and 5, male C57BL/6 mice were exposed to oxygen ions (600 MeV/n, 0.1 - 1 Gy) or protons (150 MeV, 0.5 - 1Gy) at the NASA Space Radiation Laboratory (NSRL) and transported back to UAMS for long-term follow-up. Additional groups of male C57BL/6 mice were exposed to Cesium-137 gamma rays (0.5 - 3 Gy) as a reference radiation. Oxygen ions (thus far examined up to 9 months after exposure) did not induce significant alterations in cardiac function. Nonetheless, markers of cardiac inflammatory infiltration were induced at 2 weeks, 3 months, and 9 months after exposure. Moreover, proteomic analysis has revealed that all doses of oxygen ions induced pathways of mitochondrial dysfunction and actin cytoskeleton signaling in the heart. Cardiac histological, molecular, and –omics analyses are ongoing. In addition to the ongoing mouse model studies, experiments with rat and rabbit models were initiated. Male New Zealand White rabbits and Long Evans rats were exposed to oxygen ions (600 MeV/n, 0.5 Gy) or protons (250 MeV, 0.5 Gy) at NSRL and transported back to UAMS for follow-up. These animals will be followed for 12 months after irradiation. During follow-up, cardiac function is measured with high-resolution echocardiography. Under Specific Aim 6, genomic DNA was isolated from mouse heart tissue obtained at 2 weeks and 3 months after oxygen ion exposure. Significant alterations in DNA methylation status coincided with changes in repetitive element (LINE-1) expression, suggesting that DNA methylation changes have functional consequences in the cardiac cells. To identify pathways that may contribute to the changes in DNA methylation, proteomic and metabolomic approaches are used to examine one carbon metabolism. In addition to the epigenetic studies under Specific Aim 6, fecal pellets were collected from mice exposed to oxygen ions and dose-dependent alterations in the composition of the microbiome were identified. Some of these changes in the microbiome can be related to metabolic profiles. In addition, untargeted metabolic profiling was used to identify potential biomarkers of cardiovascular radiation effects in urine and plasma samples of mice after exposure to oxygen ions. Under Specific Aim 7, cultures of mouse retinal and cardiac microvascular endothelial cells were exposed to oxygen ions, silicone ions, protons (all: 0.1 - 0.5 Gy), and Cobalt-60 gamma rays (0.1 - 2 Gy), and protein markers of endothelial cell adhesion, barrier function, and regulation of vascular tone and thrombogenesis were examined. Several protein markers show the largest response to radiation at doses below 1 Gy. In addition, tube formation was inhibited when irradiated cells were seeded on a Matrigel/collagen mixture. Studies with human retinal and cardiac microvascular endothelial cells are ongoing.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	There is renewed interest in the chronic cardiovascular effects of exposures to low doses of ionizing radiation on Earth, including exposures due to medical treatments, occupational low-dose exposures, and radiological accidents. In addition, there has been longstanding interest in gamma-tocotrienol as a potential countermeasure against radiation from a nuclear attack or accident, and our research team is involved in recently started studies for the advanced development of gamma-tocotrienol as a radiation countermeasure against accidental whole-body gamma-ray exposure. Recent clinical trials have also begun to test gamma-tocotrienol as a potential mitigator of normal tissue effects from radiotherapy in cancer treatment. The current project will elucidate chronic effects of low-dose ionizing radiation on heart and vasculature, identify biological mechanisms, and test whether gamma-tocotrienol can protect against or mitigate these effects. These studies will thereby contribute to the general understanding of the cardiovascular effects of low-dose ionizing radiation, and aid in the development of gamma-tocotrienol as a radiation countermeasure on Earth.

Task Progress:	Under studies that were performed to identify acute effects of low dose SPE-like proton exposure, a simulated SPE proton beam was developed and used to irradiate male 6 month old mice. Mouse retinal samples were collected and examined for the effects of protons on the endothelium and on apoptotic cell death. In addition, the effects of radiation on hematopoietic stem and progenitor cell function and numbers of circulating blood cells were identified. These biological responses were compared with those of gamma-rays as a reference radiation. Experiments with mouse models of proton exposure and hindlimb unloading have begun to identify potential interactions of radiation and microgravity. Under studies that were performed to determine degenerative cardiovascular effects of exposure to low dose protons and oxygen ions, mouse, rat, and rabbit models were exposed to oxygen ions, protons, or gamma-rays, and animals are followed up to 12 months after irradiation. The effects of radiation on cardiac function and structure are being characterized. Proteomic analysis has identified molecular pathways that are altered by radiation in the mouse heart. Metabolomic analysis of plasma and urine samples has started to identify potential biomarkers of cardiovascular radiation effects. Epigenetic analyses have identified effects of radiation on DNA methylation status in the heart. Lastly, experiments with cultures of mouse retinal and cardiac microvascular endothelial cells exposed to oxygen ions, silicone ions, protons, and gamma rays have started to characterize the effects of various types of radiation on protein markers of endothelial cell adhesion, barrier function, and regulation of vascular tone and thrombogenesis. Experiments with human cardiac and retinal endothelial cells have begun.
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