Fiscal Year:	FY 2015	**Task Last Updated:**	FY 07/07/2015
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) **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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Zip Code:	72205-7101	**Congressional District:**	2
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	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:	0	**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) Nelson, Gregory Ph.D. (Loma Linda University) Tackett, Alan Ph.D. (University of Arkansas for Medical Sciences)		
Grant/Contract No.:	NCC 9-58-RE03701		
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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 first year, the following progress was made: Under Specific Aim 1, the proton therapy facility at LLU was used to develop a fully modulated beam (Spread Out Bragg Peak) of 150 MeV protons for simulation of solar particle event (SPE) protons. The LLU team has harvested tissues from male C57BL/6 mice at 60 hours and 14 days after protons at doses of 0, 0.1, 0.25, or 0.5 Gy and at 48 hours and 14 days after irradiation with Cobalt-60 gamma rays as a reference radiation. First analyses of the retina indicated that proton doses of 0.25 and 0.5 Gy caused apoptosis in the outer plexiform layer, inner nuclear layer, and ganglion cell layer, suggesting that SPE-like protons may cause damage to the retina at relatively low doses. Femurs and tibiae were shipped to UAMS for the analysis of hematopoietic cell populations. Preliminary results indicate that protons at 0.5 Gy increased levels of reactive oxygen species (ROS) in hematopoietic stem cells (HSCs). Nonetheless, proton exposure 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. In discussion with the CSRR Scientific Advisory Committee and the NASA Space Radiation Element, oxygen ions were selected as a representative heavy ion for studies on Galactic Cosmic Rays (GCR). Discussions were also held with Drs. Guida, Rusek, and La Tessa of Brookhaven National Laboratory (BNL) about potential implementation and development of simultaneous multiple ion exposures (H, He, Fe, and C or O). Experiments with these exposures would be in line with NASA's desire to implement GCR simulations with multiple ions. Under Specific Aims 4 and 5, male C57BL/6 mice were exposed to oxygen ions (600 MeV/n) at doses of 0.1, 0.25, or 1 Gy at the NASA Space Radiation Laboratory (NSRL) 2015 spring run (NSRL15A). Before shipment to BNL, mice were subjected to high-resolution ultrasound and retinal microscopy for baseline cardiovascular readings. Animals were returned to UAMS for short- and long-term follow-up. The first tissue and blood samples were collected at 14 days after irradiation, and histological, molecular, and –omics analyses are ongoing. Since the rabbit model is one of the animal models that most closely resemble cardiovascular effects of ionizing radiation in human subjects, an animal protocol for the exposure of rabbits to low-dose particles at NSRL was submitted to the BNL Institutional Animal Care and Use Committee. Upon approval, the protocol will be forwarded to the BNL Modified Institutional Risk Committee. Drs. Boerma and Nelson had extensive discussions about the logistics of these studies with the BNL animal care staff. Under Specific Aim 7, primary mouse retinal and cardiac microvascular endothelial cells were obtained, and cell culture protocols were optimized for each cell type. Cell cultures will be exposed to heavy ions at NSRL. Hence, cell growth kinetics and various functional assays have been standardized for implementation at BNL. Testing of cell cultures at 24 hours to 5 days after gamma ray irradiation is in progress. In the grant's second year, the following work will be performed: Under Specific Aim 1, we will continue to collect and analyze blood and tissue samples for the determination of acute effects of low-dose SPE-like proton exposure. Under Specific Aim 2, we will start experiments in mouse models in which SPE-like proton exposure is combined with hindlimb suspension to model fluid shifts from exposure to microgravity. Under Specific Aim 4, mice that were exposed to oxygen ions in year 1 will be followed to determine late cardiovascular effects. Additional cohorts of mice will be exposed to gamma rays as a reference radiation, using the cesium source at UAMS. Under Specific Aim 5, blood and urine samples collected from both the acute and degenerative studies will be analyzed with metabolomics and proteomics, and pathway analyses will be performed to start the identification of biomarkers of radiation effects. Under Specific Aim 6, tissue samples from both the acute and degenerative studies will be analyzed with metabolomics and DNA methylation assays. Under Specific Aim 7, cultures of mouse and human primary retinal and cardiac endothelial cells will be exposed to oxygen ions at NSRL, and to gamma rays and protons at LLU. Markers of cell survival, inflammation, endothelial barrier function, and oxidative stress will be evaluated.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	There is renewed interest in the chronic cardiovascular effects of terrestrial exposures to low doses of ionizing radiation. In addition, there has been longstanding interest in gamma-tocotrienol as a potential countermeasure against radiation from a nuclear attack or accident, and gamma-tocotrienol is currently being examined 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 terrestrial radiation countermeasure.
Task Progress:	In this first grant year, progress has been made under both acute effects and degenerative tissue effects studies. First, the proton therapy facility at LLU was used to develop a fully modulated beam (Spread Out Bragg Peak) of 150 MeV protons for close simulation of SPE-like protons. The proton beam was then used for proton exposure of 6-months old male C57BL/6 mice, and progress was made towards determining the acute effects of low-dose SPE-like protons on the hematopoietic system, skin, and retina. Second, mouse models were exposed to low-dose heavy ions at NSRL, and analysis of long-term alterations in cardiac function and vascular structure is ongoing. Discussions to expose rabbits to heavy ions or protons at NSRL with BNL staff have started. Lastly, mouse cardiac and retinal microvascular endothelial cells were obtained, and two- and three-dimensional cell culture conditions were optimized. Experiments to determine the endothelial response to protons, heavy ions, and gamma rays have started.

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