

<b>Fiscal Year:</b>	FY 2017	<b>Task Last Updated:</b>	FY 01/24/2018
<b>PI Name:</b>	Boerma, Marjan Ph.D.		
<b>Project Title:</b>	Center for Research on Cardiac, Vascular, and Acute Effects of Space Radiation		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	NSBRI		
<b>Program/Discipline--Element/Subdiscipline:</b>	NSBRI--Radiation Effects Team		
<b>Joint Agency Name:</b>	<b>TechPort:</b>	No	
<b>Human Research Program Elements:</b>	(1) <b>SR</b> :Space Radiation		
<b>Human Research Program Risks:</b>	(1) <b>ARS</b> :Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs) (2) <b>Degen</b> :Risk Of Cardiovascular Disease and Other Degenerative Tissue Effects From Radiation Exposure (IRP Rev F)		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>City:</b>	Little Rock	<b>State:</b>	AR
<b>Zip Code:</b>	72205-7101	<b>Congressional District:</b>	2
<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation:</b>	2013 NSBRI-RFA-13-02 Center for Space Radiation Research (CSRR)
<b>Start Date:</b>	06/01/2014	<b>End Date:</b>	05/31/2017
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	0
<b>No. of PhD Candidates:</b>	0	<b>No. of Master' Degrees:</b>	0
<b>No. of Master's Candidates:</b>	0	<b>No. of Bachelor's Degrees:</b>	0
<b>No. of Bachelor's Candidates:</b>	1	<b>Monitoring Center:</b>	NSBRI
<b>Contact Monitor:</b>	<b>Contact Phone:</b>		
<b>Contact Email:</b>			
<b>Flight Program:</b>			
<b>Flight Assignment:</b>			
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Mao, Xiao M.D. ( 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 )		
<b>Grant/Contract No.:</b>	NCC 9-58-RE03701		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

The Center for Research on Cardiac, Vascular, and Acute Effects of Space Radiation consisted of teams of investigators from the University of Arkansas for Medical Sciences (UAMS), Loma Linda University (LLU), the University of Arizona (UAZ), and Georgetown University. We used multiple animal models to characterize acute effects of protons at doses lower than addressed in previous animal studies, and experiments involved exposure of animals and cell cultures to protons and heavy ions to examine degenerative cardiovascular effects. We pursued 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 cardiovascular effects of particle irradiation.

Key studies and findings under each Specific Aim:

1) Male C57BL/6 mice were irradiated at 6 months of age with a fully modulated 150 MeV proton beam to mimic a solar particle event (SPE) or cobalt-60 gamma-rays at doses of 0.1 – 0.5 Gy, and blood and spleen cells were quantified with a hematology analyzer and flow cytometry. Doses =0.1 Gy of both protons and gamma-rays caused a decrease in blood cell counts at 60 hours and 4 days, followed by a gradual repopulation after 1 week. These studies contribute to the determination of dose threshold for acute effects.

2) Mice were subjected to hindlimb unloading to remove mechanical loads from the posterior musculoskeletal system and generate a cephalic fluid shift, both of which occur in microgravity. Thus, animals were hindlimb unloaded for 7 days, irradiated at 0.5 Gy with modulated 150 MeV protons, and hindlimb unloaded for an additional 7 days. The most severe decrease in whole blood cell and lymphocyte counts was seen in animals exposed to both radiation and unloading (i.e., a significant interaction was seen between radiation and hindlimb unloading). Similarly, apoptosis and cellular senescence in the retina were most severe in the combined exposure group.

3) The mouse ear swelling test was used to assess adaptive immunity. Mice were challenged with an injection of FITC, followed 4 days later by modulated 150 MeV proton irradiation at a dose of 0.5 Gy. When mice were re-challenged after 2 weeks with an injection of fluorescein isothiocyanate (FITC) into one of the ears, relative ear swelling was significantly increased in the irradiated group compared with sham-irradiated animals. These results suggest that solar particle event (SPE)-like proton exposures may enhance the adaptive immune response, with potential negative consequences in hypersensitivity reactions and allergies.

4) Male C57BL/6 mice were used to determine cardiac function, tissue structure, and protein expression up to 9 months after exposure to 16O (600 MeV/n, 0.05 – 1 Gy), protons (150 MeV, 0.5 or 1 Gy), or 137Cs gamma-rays (0.5 – 3 Gy). 16O caused small but significant decreases and protons small increases in echocardiographic parameters. All 3 types of radiation induced protein markers of cardiac inflammatory infiltration at =1 Gy. Additionally, male Long Evans rats and male New Zealand White rabbits were exposed to 16O (600 MeV/n, 0.5 Gy) or protons (250 MeV, 0.5 Gy) and followed for 12 months after irradiation. Both rats and rabbits showed a small but significant increase in plasma levels of the injury marker cardiac troponin I (cTnI). In rabbits, this coincided with small increases in ejection fraction as measured with echocardiography. On the other hand, no significant changes were found in cardiac mast cell numbers or collagen deposition in any of the three species. In addition, no changes were seen in the structure of the retinal vasculature in irradiated mice. Altogether, cardiovascular effects of radiation were mild.

5) Proteomics was performed on samples of mouse left ventricle and plasma collected under Specific Aim 4. Pathways that were most commonly identified by Ingenuity Pathway Analysis included mitochondrial dysfunction, the nuclear receptor FXR/RXR pathway, and others.

6) Metabolomics was performed on samples of mouse left ventricle, plasma, urine, and feces collected under Specific Aim 4. Low doses of 16O (0.1 Gy and 0.25 Gy) induced more changes in metabolite profiles than 1 Gy. These profiles suggest inflammation, and oxidative and nitrosative stress. Alterations in one-carbon metabolism and DNA methylation pointed to potential molecular mechanisms by which oxygen ions modify the heart. Some of the changes in fecal metabolites could be attributed to radiation-induced changes in the microbiome.

7) Cultures of mouse and human retinal and cardiac endothelial cells were exposed to protons, heavy ions, and gamma-rays. Alterations in protein expressions were dependent on radiation type, dose, and cell type. In addition, doses =0.1 Gy caused a decrease in tubule network formation when cells were plated on a Matrigel/collagen matrix 6 hours after irradiation, indicative of a reduced capacity for early-onset angiogenesis.

8) Male C57BL/6 mice were exposed to 16O (600 MeV/n, 0.25 Gy) and administered gamma-tocotrienol (s.c., 50 mg/kg) once a day Monday – Friday for 4 weeks after irradiation. When measured 2 weeks after irradiation, gamma-tocotrienol reduced left ventricular protein levels of CD2 and collagen type III, but did not modify CD68 or mast cell tryptase levels. Analysis of echocardiography recordings and tissue samples at remaining post-radiation time points is being finalized.

#### Task Description:

#### 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, such as from accidental exposure or medical and diagnostic treatments. This project has assessed chronic effects of low-dose ionizing radiation on heart and vasculature and has started the identification of potential biological mechanisms. These studies will contribute to the general understanding of the cardiovascular effects of low-dose ionizing radiation. The Armed Forces Radiobiology Research Institute (AFRRI) and other government agencies have a longstanding interest in gamma-tocotrienol as a potential countermeasure against radiation from a nuclear attack or accident and has collaborated with several investigators that have also served on the current project. Results obtained from the current studies indirectly support our efforts to develop gamma-tocotrienol as a countermeasure against terrestrial radiation exposure.

	<p>This project used animal models and endothelial cell cultures to characterize acute effects of protons at doses lower than previously studied and examine degenerative cardiovascular effects of protons and oxygen ions.</p> <p>Specific Aims: 1) Define acute hematopoietic effects of low-dose protons; 2) Examine acute effects of protons in combination with simulated microgravity; 3) Evaluate effects of protons on the adaptive immune response; 4) Determine effects of heavy ions and protons on cardiac and vascular function and structure; 5) Identify 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 phenotype; 8) Test whether gamma-tocotrienol protects against cardiovascular effects of radiation.</p> <p>Key findings under each aim:</p> <ol style="list-style-type: none"> <li>1) A decrease in blood cell counts up to 4 days after protons and gamma-rays at doses =0.1 Gy in mice. These studies contribute to the determination of dose threshold for acute effects;</li> <li>2) A significant interaction between simulated microgravity and radiation on blood cell count, and apoptosis and cell senescence in the mouse retina;</li> <li>3) An enhanced adaptive immune response in mice after protons, which may have potential negative consequences in hypersensitivity reactions;</li> <li>4) Small changes in echocardiography parameters and protein markers of inflammatory infiltration in the heart of proton or oxygen ion exposed mice, rats, and rabbits. Rats and rabbits showed a small but significant increase in plasma cardiac troponin I. Mice showed no changes in retinal vascular structure months after irradiation. Altogether, cardiovascular changes were mild;</li> <li>5) Proteomics performed on samples of mouse heart and plasma revealed common pathways including mitochondrial dysfunction, the nuclear receptor FXR/RXR pathway, and others;</li> <li>6) Metabolomics performed on samples of mouse heart, plasma, urine, and feces revealed more changes after low doses of oxygen ions (0.1 Gy, 0.25 Gy) compared to 1 Gy. Alterations in one-carbon metabolism and DNA methylation pointed to potential molecular mechanisms by which oxygen ions modify the heart. Some of the fecal metabolites were attributed to radiation-induced changes in the microbiome;</li> <li>7) Cultures of mouse and human retinal and cardiac endothelial cells were exposed to protons, heavy ions, and gamma-rays. Alterations in protein expressions were dependent on radiation type, dose, and cell type. Doses =0.1 Gy caused a decrease in tubule network formation indicative of a reduced capacity for early-onset angiogenesis;</li> <li>8) Mice were administered the radiation countermeasure gamma-tocotrienol for 4 weeks after oxygen ion irradiation. At 2 weeks, gamma-tocotrienol reduced cardiac protein levels of CD2 and collagen type III, but not of CD68 or mast cell tryptase. The analysis of cardiac function and cardiac tissue structure is ongoing.</li> </ol>
<b>Task Progress:</b>	
<b>Bibliography Type:</b>	Description: (Last Updated: 09/19/2019)
<b>Articles in Peer-reviewed Journals</b>	Chang J, Luo Y, Wang Y, Pathak R, Sridharan V, Jones T, Mao XW, Nelson G, Boerma M, Hauer-Jensen M, Zhou D, Shao L. "Low doses of oxygen ion irradiation cause acute damage to hematopoietic cells in mice." PLoS One. 2016 Jul 1;11(7):e0158097. eCollection 2016. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/27367604/">PMID: 27367604</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC4930193/">PMCID: PMC4930193</a> , Jul-2016
<b>Articles in Peer-reviewed Journals</b>	Pathak R, Wang J, Garg S, Aykin-Burns N, Petersen KU, Hauer-Jensen M. "Recombinant thrombomodulin (Solulin) ameliorates early intestinal radiation toxicity in a preclinical rat model." Radiat Res. 2016 Aug;186(2):112-20. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/27459702/">PMID: 27459702</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC4995594/">PMCID: PMC4995594</a> , Aug-2016
<b>Articles in Peer-reviewed Journals</b>	Wang Y, Boerma M, Zhou D. "Ionizing radiation-induced endothelial cell senescence and cardiovascular diseases." Radiat Res. 2016 Aug;186(2):153-61. Review. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/27387862/">PMID: 27387862</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC4997805/">PMCID: PMC4997805</a> , Aug-2016
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<b>Articles in Peer-reviewed Journals</b>	Carr H, Alexander TC, Groves T, Kiffer F, Wang J, Price E, Boerma M, Allen AR. "Early effects of 16O radiation on neuronal morphology and cognition in a murine model." Life Sciences in Space Research. 2018 May;17:63-73. Epub 2018 Mar 14. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/29753415/">PMID: 29753415</a> , May-2018
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Awards	Tackett A. (Alan Tackett) "Scharlau Family Endowed Chair, December 2016." Dec-2016
Awards	Boerma M. (Marjan Boerma) "Radiation Research Society J.W. Osborne Award, October 2016." Oct-2016
Awards	Hauer-Jensen M. (Martin Hauer-Jensen) "J. Thomas May Distinguished Endowed Chair, August 2016." Aug-2016