Fiscal Year:	FY 2019	**Task Last Updated:**	FY 03/19/2019
PI Name:	Baker, John Ph.D.		
Project Title:	Determination of Risk for and Occurrence of Heart Disease from Space 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		
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PI Organization Type:	UNIVERSITY	**Phone:**	414-955-8706
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PI Web Page:			
City:	Milwaukee	**State:**	WI
Zip Code:	53226-3548	**Congressional District:**	5
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-RADIATION
Start Date:	01/08/2015	**End Date:**	01/07/2019
No. of Post Docs:	0	**No. of PhD Degrees:**	3
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:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	March 2019: There have been no changes to the PI or other key personnel. November 2016: There have been no changes to the PI or other key personnel.		
COI Name (Institution):	Kronenberg, Amy D.Sc. (Lawrence Berkeley National Laboratory)		
Grant/Contract No.:	NNX15AD69G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The objective of this application is to determine the increased risk of developing degenerative cardiac disease because of exposure to representative components of space radiation. Ground-based animal studies will be used to assess the increased risk for developing degenerative cardiovascular disease. A model of accelerated coronary fibrosis and the degeneration of heart morphology and function following exposure to ionizing radiation, in previously healthy rats, has already been developed and validated. In this rat model, whole body ionizing radiation with a single dose of 10 Gy of X-rays resulted in clinically relevant changes in cardiac function that can be measured, noninvasively. Our central hypothesis is that whole body exposure to space-relevant doses of galactic cosmic rays (GCRs) will increase the risk for developing degenerative cardiovascular disease. Three Specific Aims are proposed to directly address the issue of cardiovascular risk using experimental approaches in a rat model of disease progression to apply the results from the rat studies to astronauts. The proposed investigations directly address important aspects of the NASA Human Research Program (HRP) Degenerative Tissue Gaps, as set forth in the Human Research Roadmap. HRP gaps are identified that are addressed by each Specific Aim. The proposed research will provide important information to help close these gaps. Specific Aim 1: Determine the progression rates, latency periods for single beams of iron ions, silicon ions, and protons of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of GCRs. (HRP Gaps Degen-1, -2, and -3). Specific Aim 2: Determine the progression rates, latency periods for gamma rays of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of gamma radiation so that relative biological effectiveness can be estimated. (HRP Gaps Degen-1, -2, and -3). Specific Aim 3: Determine the progression rates, latency periods for mixed beams of iron ions, silicon ions, and protons of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of GCRs. (HRP Gaps Degen-1, -2, and -3).
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research benefits life on Earth as it relates to patients who receive therapeutic radiation for the treatment of cancer and to individuals who receive accidental exposure to radiation from a nuclear accident.
	FINAL REPORTING MARCH 2019 This project addresses the following goals set forward in the 2014 NASA NRA (NASA Research Announcement) for Radiation Studies: 1) to provide detailed physiological and bio-molecular characterization of degenerative tissue responses to space-like radiation doses that are mission relevant for future human spaceflight outside low Earth orbit and 2) to determine relative biological effectiveness (RBE) values for space radiations in appropriate animals using relevant intermediate as well as late physiological endpoints and effects. These experimentally derived RBE values will be used to provide quantitative inputs into methods and models to calculate degenerative tissue responses in humans following exposures in space. The objective of this application is to determine the increased risk of developing degenerative cardiac disease because of exposure to representative components of space radiation. Ground-based animal studies will be used to assess the increased risk for developing degenerative cardiovascular disease. A model of accelerated coronary fibrosis and the degeneration of heart morphology and function following exposure to ionizing radiation, in previously healthy rats, has already been developed and validated. In this rat model, whole body ionizing radiation with a single dose of 10 Gy of X-rays resulted in clinically relevant changes in cardiac function that can be measured, noninvasively. Our central hypothesis is that whole body exposure to space-relevant doses of galactic cosmic rays (GCRs) will increase the risk for developing degenerative cardiovascular disease. The central hypothesis of this project is that whole body exposure to space-relevant doses of galactic cosmic rays (GCRs) will increase the risk for developing degenerative cardiovascular disease. Three Specific Aims were proposed to directly address the issue of cardiovascular risk using experimental approaches in a rat model of disease progression to apply the results from the rat studies to astronauts. The proposed investigations directly address important aspects of the NASA Human Research Program (HRP) Degenerative Tissue Gaps, as set forth in the Human Research Roadmap. HRP gaps are identified that are addressed by each Specific Aim. The proposed research will provide important information to help close these gaps. Specific Aim 1: Determine the progression rates, latency periods for single beams of iron ions, silicon ions, and protons of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of GCRs. (HRP Gaps Degen-1, -2, and -3). Specific Aim 2: Determine the progression rates, latency periods for gamma rays of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of gamma radiation so that relative biological effectiveness can be estimated. (HRP Gaps Degen-1, -2, and -3). Specific Aim 3: Determine the progression rates, latency periods for mixed beams of iron ions, silicon ions, and protons of risk for and occurrence of degenerative disease in the cardiovascular system resulting from ground-based studies of GCRs. (HRP Gaps Degen-1, -2, and -3). Following irradiation of the rats (n=12 per group) we have determined changes in risk factors for cardiovascular disease and cardiac injury in a longitudinal study. The end points measured included total cholesterol and triglycerides in blood, clinically accepted biomarker of risk for cardiovascular disease. These measurements were made monthly over a 9 month follow up period. We performed histological studies and cardiac echocardiography studies to measure injury to the heart at the end of the study. We used this data to determine dose-response relationships for single beams 56Fe, 28Si, and protons and mixed beams of 56Fe, 28Si, and protons as representative ions in GCRs. The relationship between dose for particles (56Fe, 28Si, or protons), compared with gamma-rays as the reference radiation, were determined for changes in risk factors for cardiac disease (cholesterols and triglycerides), cardiovascular injury (radial and circumferential strain using echocardiography), and renal injury (blood urea nitrogen and blood pressure) following whole body irradiation. Dose-response relationships were established for renal disease. Male Wistar rats were exposed to mixed beams 1 GeV protons (80% of the total dose to each subject), 500 MeV/n Si ions (10% of the total dose to each subject), and 600 MeV/n Fe ions (10% of the total dose to each subject). Our five dose groups were: 0, 0.25 Gy, 0.5 Gy, 0.75 Gy, and 1.5 Gy, dose rate 50 cGy/min. Exposure of rats to 1.5 Gy of

Task Progress:	simulated GCRs increased perivascular collagen content by 148% compared with sham-irradiated, age-matched controls after 270 days. These findings identify a cardiac vascular pathology resulting from exposure to representative components of GCRs. Irradiation of WAG rats with 0.25 Gy, 0.5 Gy, and 0.75 Gy of mixed field beams showed no increase above baseline levels for perivascular collagen content compared with sham-irradiated, age-matched rats after 270 days. These findings provide evidence of a threshold dose for cardiac fibrosis resulting from exposure to representative components of GCRs. Total cholesterol and triglyceride levels in sham-irradiated rats progressively increased over the 270-day study period compared with values at 30 days but each was essentially unchanged in gamma-ray exposed rats when compared with age-matched sham-irradiated controls. Coronary vessels and cardiomyocytes from rats exposed to even the highest dose of 6.0 Gy of gamma-rays remained normal in appearance compared with hearts from age-matched, sham-irradiated rats. There was no increase in cardiac perivascular collagen deposition in irradiated hearts compared with age-matched sham-irradiated controls. Blood urea nitrogen and creatinine levels were largely unchanged in sham-irradiated rats over the 270-day study period, and these levels were also unchanged over the 270 day follow up period for all the gamma-irradiated rats. Cortex and medulla from rats 270 days after exposure to 6.0 Gy of gamma-rays remained normal in appearance compared with kidneys from age-matched, sham-irradiated rats. Systemic blood pressure (systolic and diastolic) was not significantly elevated over the 270-day period following whole body exposure to gamma-rays. • There have been no deaths associated with any dose of radiation. • Risk factors for cardiac disease and renal injury were essentially unchanged after exposure of rats to individual beams of protons, 28Si ions, and 56Fe ions over the 270 day follow up period. • Rats exposed to mixed beams of protons, 28Si ions, and 56Fe ions showed modest changes in risk for cardiac disease and kidney injury after irradiation and increased perivascular collagen deposition at the end of the 270 day follow up period. • We monitored early changes (30 days and 60 days after irradiation) for the same oxidative and inflammatory biomarkers in rats as those currently being evaluated in astronauts aboard the ISS. Biomarkers of oxidative stress and inflammation increased 30 days after irradiation and decreased 60 days after irradiation with mixed beams. Our studies are starting to provide an estimation for the occurrence of cardiac disease after exposure to representative components of space radiation that will enable NASA to evaluate permissible exposure limits. ANNUAL REPORTING NOVEMBER 2018: This project addresses the following goals set forward in the 2014 NASA NRA (NASA Research Announcement) for Radiation Studies: 1) to provide detailed physiological and bio-molecular characterization of degenerative tissue responses to space-like radiation doses that are mission relevant for future human spaceflight outside low Earth orbit and 2) to determine relative biological effectiveness (RBE) values for space radiations in appropriate animals using relevant intermediate as well as late physiological endpoints and effects. These experimentally derived RBE values are to provide quantitative inputs into methods and models to calculate degenerative tissue responses in humans following exposures in space. The central hypothesis of this project is that whole body exposure to space-relevant doses of galactic cosmic rays (GCRs) will increase the risk for developing degenerative cardiovascular disease. Three specific aims are proposed to address the issue of cardiovascular risk using experimental approaches in a rat model and the mathematical modeling of rat and human data relevant to the research questions. Specific Aim 1: Determine the progression rates, latency periods and relative biological effectiveness (RBE) of iron ions, silicon and protons compared to gamma-rays for degenerative disease in the cardiovascular system resulting from ground-based exposure to GCRs. Specific Aim 2: Determine the importance of the kidney in the mechanisms underlying cardiac disease from HZE ion exposure. Specific Aim 3: Develop a theoretical model of disease progression to extrapolate the results for charged particle-induced cardiac risks in rats to degenerative cardiac disease in astronauts. Following irradiation of the rats (n=12 per group) we are determining changes in risk factors for cardiovascular disease and cardiac injury in a longitudinal study. The end points to be measured include total cholesterol, HDL-cholesterol, and triglycerides in blood. These measurements will be made monthly over a 9 month follow up period. We performed histological studies and cardiac echocardiography studies to measure injury to the heart at the end of the study. We are using this data to determine dose-response relationships for 56Fe, 28Si, and protons as representative ions in GCRs. Male Wistar rats have been exposed to mixed beams 1 GeV protons (80% of the total dose to each subject), 500 MeV/n Si ions (10% of the total dose to each subject), and 600 MeV/n Fe ions (10% of the total dose to each subject). Our five dose groups were: 0, 0.25 Gy, 0.5 Gy, 0.75 Gy, and 1.5 Gy, dose rate 50 cGy/min. Significant findings • There have been no deaths associated with any dose of radiation, • Risk factors for cardiac disease and renal injury were essentially unchanged after exposure of rats to individual beams of protons, 28Si ions, and 56Fe ions over the 270 day follow up period, • Rats exposed to mixed beams of protons, 28Si ions, and 56Fe ions showed modest changes in risk for cardiac disease and kidney injury after irradiation and increased perivascular collagen deposition at the end of the 270 day follow up period, • Biomarkers of oxidative stress and inflammation increased 30 days after irradiation and decreased 60 days after irradiation with mixed beams, • No increase in risk factors for cardiac disease after exposure to gamma radiation.
Bibliography Type:	Description: (Last Updated: 02/20/2025)

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