Fiscal Year:	FY 2013	**Task Last Updated:**	FY 12/07/2012
PI Name:	Kucik, Dennis F. M.D., Ph.D.		
Project Title:	Mechanisms, early events, and dose dependence of radiation-induced atherosclerosis		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
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:	35205-4831	**Congressional District:**	7
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2009 Space Radiobiology NNJ09ZSA001N
Start Date:	02/01/2011	**End Date:**	07/31/2015
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**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
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/31/2015 per PI and NSSC information (Ed., 8/27/14) NOTE: End date changed to 7/31/2014 per NSSC information (Ed., 4/10/14) NOTE: End date changed to 4/30/2014 per NSSC information (Ed., 1/22/14)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Kabarowski, Janusz Ph.D. (University of Alabama at Birmingham)		
Grant/Contract No.:	NNX11AC61G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Radiation causes vascular inflammation, which is a known risk factor for atherosclerosis. Epidemiological studies have shown that radiation from many sources, including cancer treatments, atomic bombs, and excessive occupational exposure all increase the risk for atherosclerosis. Previous studies, using gamma and/or X-ray radiation, have demonstrated that radiation causes increased white blood cell (WBC) adhesion to the blood vessel wall, an essential early event in atherosclerotic plaque formation. What is not known is whether the cosmic radiation astronauts will be exposed to on missions to the moon and Mars will similarly increase the risk for atherosclerosis. In our last project, we established that X-ray, 56Fe (iron ion) and proton irradiation of blood vessel cells increase adhesiveness of the vessel wall, and that X-rays and 56Fe accelerate development of atherosclerosis in a mouse model (results of proton experiments are pending). The molecular mechanism for this, however, is not yet known. In addition, it remains to be determined how fractionation of doses and irradiation of other tissues affect the dose dependence of both cell adhesion and development of atherosclerosis. With the hypothesis that radiation in general and cosmic radiation in particular directly alter the adhesive properties of vascular endothelium, and resultant vascular inflammation accelerates atherosclerosis, we propose to systematically investigate mechanisms of radiation effects on vascular cells, using both isolated cells and whole mice, to better predict risk and to provide the basis to develop possible future countermeasures. Our specific aims are: Aim 1: Determine whether atherogenic effects of radiation are limited to local effects on vascular endothelium, or if other systems contribute to disease progression and/or modify dose dependence. Aim 2: Determine the molecular mechanism of acute activation of leukocyte-endothelial cell adhesion in response to radiation. Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Therapeutic radiation is a well-established risk factor for cardiovascular disease and stroke. Head and neck cancer patients who undergo radiation treatment are at significantly elevated risk of stroke, even in young patients whose risk would otherwise be near zero. For women with early breast cancer, the benefit of radiotherapy can be nearly offset by the increased risk of mortality from vascular disease. Moreover, new modalities of therapeutic radiation include the use of proton and carbon ion irradiation. Little is known about the adverse effects of these types of radiation, but early results from cell and animal studies suggest that the consequences for cardiovascular disease could be equal to or greater than those for gamma- and X-rays. The risk from accidental exposure is similar. For example, atomic bomb survivors have an increased incidence of coronary artery disease and stroke. Risk for cardiovascular disease after radiation exposure at Chernobyl was increased for those who were exposed to less than 1 Gy. Even radiation technologists in the 1950s (when shielding was less rigorous) had an increased risk of death from cardiovascular disease, demonstrating that repeated exposure at low doses results in significant risk years later. Currently, the principal strategy for reducing risk is avoidance of exposure. Completion of our specific aims will advance the knowledge of the molecular mechanisms of radiation-induced atherosclerosis, enabling better prediction of cardiovascular risk from exposure, facilitating early detection through the use of surrogate biomarkers, and pointing the way toward potential countermeasures to mitigate the cardiovascular consequences of radiation exposure, both in space and on Earth.
Task Progress:	Aim 1: Determine whether atherogenic effects of radiation are limited to local effects on vascular endothelium, or if other systems contribute to disease progression and/or modify dose dependence. We had established in our last project that 2-5 Gy 56Fe targeted to the upper aorta and the carotid arteries of 10-week old apoE -/- mice accelerated the development of atherosclerosis by 13 weeks post-irradiation. This radiation dose is 4-8 times lower than the X-ray dose required to produce the same effect in this well-characterized mouse atherosclerosis model. Atherosclerosis was exacerbated in irradiated portions of the aorta, but not in un-irradiated portions of the same vessel, indicating that at least part of the mechanism for radiation-induced atherosclerosis is a direct effect on the vessels. It is important now to take this to the next level of complexity and determine whether effects on extravascular systems also contribute to atherosclerosis progression. We have been conducting experiments at NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL) to compare pro-atherogenic effects of whole-body irradiation to irradiation of the major vessels only. As expected, whole body irradiation results in a more widespread pattern of promotion of atherosclerotic plaques. There are, however, differences in the formerly-targeted areas (the upper aorta and carotid arteries) as well. We are working to characterize these differences and to understand the mechanism by which development of atherosclerotic plaques in a particular region of a vessel might be influenced by indirect effects of radiation delivered elsewhere. Aim 2: Determine the molecular mechanism whereby radiation leads to activation of leukocyte-EC adhesion. Radiation increases the adhesiveness of vascular endothelial cells, an important, early step in the development of atherosclerosis. This year, we published results demonstrating that x-ray induced endothelial adhesiveness can occur even without a change in the expression level of pro-atherogenic adhesion molecules. That is, even though endothelial cell adhesiveness was increased by radiation, cell surface expression of key endothelial adhesion molecules did not significantly increase. We then showed that the increased adhesiveness was due to signaling by the endothelial cells to the leukocytes, activating receptors on the leukocytes to increase adhesion between the two cell types. We have now completed experiments demonstrating that iron ion radiation, an important component of cosmic radiation that is very different from x-rays, also increases endothelial cell adhesiveness by a chemokine-dependent mechanism. Studies are underway to further clarify the similarities and differences between x-ray and iron ion effects to determine whether other knowledge about the mechanism of action of x-rays can also be used to understand the potentially pro-atherogenic effects of cosmic radiation. Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints. In November, 2012, we performed an experiment in which 10-week old male mice were either un-irradiated, irradiated with a single dose of 2 Gy iron ions, or irradiated with 5 doses of 0.4 Gy iron ions each on 5 consecutive days. These mice will be raised under standard conditions and fed a normal diet until they are analyzed at 13 weeks post-irradiation.

Bibliography Type:	Description: (Last Updated: 04/12/2018)
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