Fiscal Year:	FY 2012	**Task Last Updated:**	FY 12/02/2011
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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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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2009 Space Radiobiology NNJ09ZSA001N
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Flight Program:			
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Key Personnel Changes/Previous PI:			
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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

Task Description:	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 23 weeks of age. 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. The purpose of targeting the radiation was to exclude effects on other organs and on the immune system which might contribute to the disease process and cloud interpretation of direct effects. However, since astronauts will receive whole-body 56Fe irradiation on interplanetary missions, 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. To address this question, 10-week old apoE -/- mice were exposed to 2-5 Gy full body 56Fe irradiation in May, 2011 and were dissected 13 weeks later. Aortic en face preparations and aortic root and carotid artery cross sections were prepared for histologic analysis as had been done previously for targeted radiation experiments. Analysis is currently being performed to determine whether disease progression in the aortic arch and carotid arteries is modified by irradiation of the remainder of the animal. Aim 2:Determine the molecular mechanism whereby radiation leads to activation of leukocyte-EC adhesion. This year, we published results demonstrating that radiation-induced adhesiveness is not due to increased expression of adhesion molecules, but is a result of chemokine-dependent signaling from the endothelial cell to the leukocyte. That is, even though endothelial cell adhesiveness was increased, cell surface expression of key endothelial adhesion molecules, including ICAM-1, VCAM-1, E-selectin, and P-selectin, did not significantly increase following irradiation (as measured by flow cytometry). Blocking the leukocyte receptors for ICAM-1 and VCAM-1, however, abrogated the radiation-induced adhesiveness. Since these receptors are integrins, a group of adhesion molecules that exist in multiple activation states, we checked whether integrin activation played a role in radiation-induced adhesion. Pre-treatment of the leukocytes with pertussis toxin, which blocks chemokine-dependent integrin activation, blocked the increased endothelial cell-leukocyte adhesion. Since the endothelial cells were irradiated, but the leukocytes were not, this suggests that radiation stimulated chemokine signaling by the endothelial cells to the leukocytes, activating integrins on the leukocytes to increase adhesion between the two cell types. This year, we have identified several endothelial cell-expressed chemokines that seem to be involved in this mechanism. Experiments are currently underway to determine the relative importance of trans-membrane chemokines, anchored in the cell membrane, and those that are secreted to bind to carbohydrates on the cell surface. Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints. Awaiting identification of surrogate endpoints.
Bibliography Type:	Description: (Last Updated: 04/12/2018)

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