

<b>Fiscal Year:</b>	FY 2013	<b>Task Last Updated:</b>	FY 12/07/2012
<b>PI Name:</b>	Kucik, Dennis F. M.D., Ph.D.		
<b>Project Title:</b>	Mechanisms, early events, and dose dependence of radiation-induced atherosclerosis		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	HUMAN RESEARCH		
<b>Program/Discipline--Element/Subdiscipline:</b>	HUMAN RESEARCH--Radiation health		
<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>Cardiovascular:</b> Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
<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>Zip Code:</b>	35205-4831	<b>Congressional District:</b>	7
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<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Kabarowski, Janusz Ph.D. ( University of Alabama at Birmingham )		
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<b>Performance Goal Text:</b>			

	<p>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, <sup>56</sup>Fe (iron ion) and proton irradiation of blood vessel cells increase adhesiveness of the vessel wall, and that X-rays and <sup>56</sup>Fe 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.</p> <p><b>Task Description:</b></p> <p>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:</p> <p>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.</p> <p>Aim 2: Determine the molecular mechanism of acute activation of leukocyte-endothelial cell adhesion in response to radiation.</p> <p>Aim 3: Determine how fractionation of doses affects dose-dependence of progression rates, latency periods, and surrogate endpoints.</p>
<p><b>Rationale for HRP Directed Research:</b></p>	<p>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.</p> <p>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.</p> <p>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.</p>
<p><b>Task Progress:</b></p>	<p>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 <sup>56</sup>Fe targeted to the upper aorta and the carotid arteries of 10-week old apoE<sup>-/-</sup> 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.</p> <p>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.</p> <p>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.</p>

Bibliography Type:	Description: (Last Updated: 04/12/2018)
<b>Abstracts for Journals and Proceedings</b>	Yu T, Gupta KB, Wu X, Khaled SF, Yu S, Kabarowski JH, Kucik DF. "Severity of 56Fe radiation-induced atherosclerosis is independent of serum cholesterol levels." 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. 2012 NASA Human Research Program Investigators' Workshop, Houston, TX, February 14-16, 2012. , Feb-2012
<b>Abstracts for Journals and Proceedings</b>	Gupta KB, Khaled SF, Kucik DF, Wu X, Yu T. "Adhesiveness of aortic endothelium in response to high-LET radiation is chemokine dependent." American Statistical Association (ASA) Conference on Radiation and Health, Kennebunkport, ME, June 10-13, 2012. American Statistical Association (ASA) Conference on Radiation and Health, Kennebunkport, ME, June 10-13, 2012. Meeting proceedings. <a href="http://www.amstat.org/meetings/radiation/2012/AbstractDetails.cfm?AbstractID=302254">http://www.amstat.org/meetings/radiation/2012/AbstractDetails.cfm?AbstractID=302254</a> , Jun-2012
<b>Abstracts for Journals and Proceedings</b>	Kucik DF, Yu T, Gupta KB, Wu X, Yu S, Kabarowski JH. "Severity of 56Fe Radiation-Induced Atherosclerosis in the ApoE -/- Mouse Model Is Independent of Plasma Cholesterol Levels." Life in Space for Life on Earth. European Space Agency (ESA) and International Society for Gravitational Physiology (ISGP) Joint Life Science Meeting, Aberdeen, United Kingdom, June 18-22, 2012. Published in meeting proceedings. Life in Space for Life on Earth. European Space Agency (ESA) and International Society for Gravitational Physiology (ISGP) Joint Life Science Meeting, Aberdeen, United Kingdom, June 18-22, 2012. , Jun-2012
<b>Abstracts for Journals and Proceedings</b>	Kucik DF, Gupta KB, Khaled SF, Wu X, Yu T. "Adhesiveness of aortic endothelium in response to high-LET radiation is chemokine dependent." 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. 23rd Annual NASA Space Radiation Investigators' Workshop, Durham, NC, July 8-11, 2012. , Jul-2012
<b>Abstracts for Journals and Proceedings</b>	Yu T, Gupta KB, Wu X, Khaled SF, Yu S, Kabarowski JH, Kucik DF. "Local factors modify the dose dependence of 56Fe-induced atherosclerosis. " Committee on Space Research (COSPAR) 2012 39th Scientific Assembly, Mysore, India, July 14-22, 2012. Committee on Space Research (COSPAR) 2012 39th Scientific Assembly, Mysore, India, July 14-22, 2012. , Jul-2012
<b>Abstracts for Journals and Proceedings</b>	Kucik DF, Gupta K, Khaled S, Wu X, Yu, T. "Adhesiveness of aortic endothelium in response to high-LET radiation is chemokine dependent." Annual meeting of the American Society for Gravitational and Space Research, New Orleans, LA, November 28-December 2, 2012. Program and abstracts. American Society for Gravitational and Space Research, New Orleans, LA, November 28-December 2, 2012. , Dec-2012
<b>Articles in Peer-reviewed Journals</b>	Khaled S, Gupta KB, Kucik DF. "Ionizing radiation increases adhesiveness of human aortic endothelial cells via a chemokine-dependent mechanism." Radiat Res. 2012 May;177(5):594-601. Epub 2011 Nov 15. PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/22087741/">PMID: 22087741</a> , May-2012
<b>Articles in Peer-reviewed Journals</b>	Yu T, Yu S, Gupta K, Wu X, Khaled S, Kabarowski JHS, Kucik DF. "Severity of atherosclerosis in apoE -/- mice following 56Fe irradiation is independent of plasma cholesterol levels." Gravitational and Space Biology. 2012 Apr;26(1):41-4. <a href="http://gravitationalandspacebiology.org/index.php/journal/article/view/560/586">http://gravitationalandspacebiology.org/index.php/journal/article/view/560/586</a> ; accessed 12/10/2012. , Apr-2012