Fiscal Year:	FY 2007	**Task Last Updated:**	FY 08/06/2007
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Project Title:	Human endothelial cells in 2-D and 3-D systems; non-cancer effects and space-related radiations		
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:	10032-3702	**Congressional District:**	15
Comments:			
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Contact Monitor:		**Contact Phone:**	
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Flight Program:			
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Task Description:	Though not prone to carcinogenic change the endothelial cell is of critical importance to the normal functioning of all tissues and organs of the body. Endothelial cells constitute the linings of the blood circulatory system, and disruption of this function can lead to multiple changes, from minor to catastrophic. Cardio-vascular diseases are the leading cause of death in developed societies. Endothelial cells have been studied in monolayers [2-dimensional] for many years, however it is clear that cell behavior in the third dimension [tissue-like structures] is not necessarily well represented by such studies. Recognizing the crucial role of the endothelial cell we studied the radiation sensitivity of the chromosomes of normal human umbilical vein endothelial cells [HUVEC] to low LET radiation. It was determined that chromatid-type aberrations in late G2 cells were exquisitely linearly sensitive to radiation doses in the range 0.0125 to 0.8 Gy. This response was ~ 3 times more sensitive than that of early-mid G2 cellls, and ~15 times more sensitive than for chromosome-type aberrations in non-cycling G1 cells [dose range, 0.5-8.0 Gy]. Recently we have obtained 3-dimensional capillary like tubular structures from the culture of HUVECs in collagen gel matrices. We propose to irradiate 2D [cell monolayers] and 3D [capillary-like cell structures] with Fe ions at 1GeV with doses where a bystander effect may apply [< 0.1 Gy] to doses where multiple traversals are expected [up to 1Gy]. We will compare responses to low LET X-rays and to alpha particles at the same LET as the Fe ions, where delta rays are less likely to be influential. Chromosomal changes using G2-PCC`s and state of the art m-FISH, micronuclei, apoptosis and cell-cell, cell-matrix interacting proteins will be quantified. We hypothesize that 2D versus 3D culture results in no difference in the responsiveness of human endothelial cells. We further hypothesize that space related radiations are not more effective than low LET radiations for these cells with their crucial role in the maintenance of normal bodily functions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Understanding the effects of ionizing radiation on the human endothelial cell and its consequences may aid in assessing the impact of diseases involving the circulatory system in general.
Task Progress:	The ionizing radiations to which humans are likely to be exposed in a space environment are rarely encountered in an earth environment. These consist largely of energetic low LET [linear energy transfer protons] and high LET fe ions. Little is known about the effects of space radiations on endothelial cells, the cells that provide the underpinning of the circulatory system. This study is aimed at understanding the effects of space radiations on endothelial cells using 2-dimensional [2D] and 3D culture systems of human umbilical vein endothelial cells [HUVEC]. Monolayers are being used to investigate the effect of these radiations on chromosome damage and would thus be of importance to cycling endothelial cells. Since atomic bomb survivors show non-cancer disease mortality including vascular diseases, a 3D tissue model is being used to determine the effects of space radiation on blood vessel formation and maintenance. Both high LET Fe ions and low LET protons, in addition to gamma radiation cause chromosome damage in HUVECS growing in 2D cultures. mFISH is being used to identify chromosome specific aberrations. For example, in response to 0.8 Gy Fe ions, cells showed a large number of aberrations [94% of cells] involving primarily chromosomes 1, 2, 4, 5, 7, 7, 9, and X. These include stable aberrations such as reciprocal translocations. Endothelial cells [HUVEC`s] have been successfully cultured in 3D matrices, and in the presence of appropriate growth factors found to differentiate and assemble into capillary tubes. Cells were fluorescently labelled with a long-live cyto-tracker, suspended in collagen gels and stimulated to differentiate and form vessels. Live 3D imaging of cells showed distinct stages of development starting with the formation of vacuoles, followe by cell elongation and cellular coalecence leading to the formation of capillary tube structures. Having established this scenario the effects of space-related radiations on vessel formation from individual cells, and the integrity of mature vessels was assessed. Irradiation of cells while dividing showed that a dose of 0.2 Gy of Fe ions can cause a significant decrease in vessel formation. Irradiation of mature vessels revealed that they were much more sensitive to Fe ions than they were to low LET protons. Doses of 0.8 to 1.6 Gy causing significant loss of vessel integrity, while after the highest dose of protons [3.2 Gy], vessels were indistiguishable from controls. Formed vessels are also highly resitant to gamma radiation, with limited effects at doses up to 16 Gy. A technique was developed to monitor cellular apoptosis in the 3D cultures , along with the 2D system and will be applied to radiation-type comparisons in the future. The appproach outlined has succeeded in providing the first information on the effects of space related radiations on human endothelial cells in a 3D tissue configuration. There are clear differences between the effectiveness of different radiations in these non-dividing differentiated cells. The meaning, and the mechanistic bases of these findings will be explored in future cycles, and will lead to assessments of potential consequences to the cardio-vascular system of the space traveller.
Bibliography Type:	Description: (Last Updated: 06/03/2013)