Fiscal Year:	FY 2011	**Task Last Updated:**	FY 06/03/2013
PI Name:	Geard, Charles Ray Ph.D.		
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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City:	New York	**State:**	NY
Zip Code:	10032-3702	**Congressional District:**	15
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2004 Radiation Biology NNH04ZUU005N
Start Date:	10/01/2005	**End Date:**	09/30/2011
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: Change in Gaps per HRR information (Ed., 9/26/2011) NOTE: Received no-cost extension to 9/30/2011 per C. Guidry/JSC (10/2010) NOTE: Received no-cost extension to 9/30/2010 per J. Dardano/JSC (8/09)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Grabham, Peter (Columbia University) Hu, Burong (Columbia University) Ponnaiya, Brian (Columbia University)		
Grant/Contract No.:	NNJ05HI37G		
Performance Goal No.:			
Performance Goal Text:			

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. We have successfully developed 3-D human micro-vasculature models from normal human umbilical vein endothelial cells. These structures have been characterized by multi- photon microscopy and have been irradiated with high energy iron ions and protons. Irradiation of mature vessels led to a breakdown of the vessels after low doses of iron ions [<1 Gy] but no effect of protons out to 3.2 Gray. Monitoring vessel structures over time led to the observation that the 3-D mature vessel network is essentially restored by 12 days, even after 3.2 Gy of iron ions. By contrast the irradiation of developing vessels showed that both protons and iron ions at 1GeV similarly disrupt network vessel development, with ~50% loss of intact vessel length [relative to control] at 3 days after 0.8 Gy. The full pattern of vessel recovery remains to be determined. DNA damage foci [53BP-1] formation was examined in endothelial cell nuclei in 2-D monolayers and in the cell nuclei of the 3-D micro-vasculature structures. Both protons at 0.22 keV/micrometer and Fe ions at 150 keV/micrometer showed similar kinetics of foci formation with peak yields at 1 hr and a 10 fold decline at 48hrs. However there were dramatic differences in the efficiency of focus formation. At the peak there was ~ one 53 BP-1 focus for each Fe ion traversal and ~ 1 focus for every 1,000 proton traversals. Human endothelial cells can form 3-D micro-vasculature like structures and show quantitative morphological and DNA damage responses after space-like radiations at moderate to high doses. At the fluences likely to be experienced in cells by man in space the question might reasonably be asked about the micro-vasculature; does this matter? Probably not.
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:	[Editor's note 6/3/2013: No Task Book report received. Progress section and Bibliography compiled from PI's Final Technical Report.] The most significant achievement from the body of work carried out under support from this grant was the development and introduction to space radiation biology of a human model tissue system. Normal human endothelial cells were encouraged to develop into the capillary-like structures of the human circulatory system. At various stages of development these structures were exposed to proscribed doses of energetic iron particles or protons as found in space, and responses assessed. Along with continued participation in national and international meetings where information was presented and encouragingly discussed, three peer reviewed publications resulted. The last of these was published in June 2012, after submission in December 2011, and acceptance in March 2012. Two highlights resulting from the publications are worth of note. The paper published in the International Journal of Radiation Biology in June 2012 was accorded the honor of having a representative figure of treated capillary structures from the manuscript on the front cover. The paper published in the journal, Radiation Research, in January 2011, was chosen by members of the Radiation Research Society as the most scientifically compelling of the issue. This led to an interview by Marjan Boerman, a student representative, with the PI and colleague Dr. Peter Grabham. The interview is available as a Podcast from the Radiation Research Society.
Bibliography Type:	Description: (Last Updated: 06/03/2013)
Articles in Peer-reviewed Journals	Grabham P, Hu B, Sharma P, Geard C. "Effects of ionizing radiation on three-dimensional human vessel models: differential effects according to radiation quality and cellular development." Radiat Res. 2011 Jan;175(1):21-8. Epub 2010 Nov 4. PMID: 21175343 , Jan-2011
Articles in Peer-reviewed Journals	Grabham P, Bigelow A, Geard C. "DNA damage foci formation and decline in two-dimensional monolayers and in three-dimensional human vessel models: Differential effects according to radiation quality." International Journal of Radiation Biology. 2012 Jun;88(6):493-500. Epub 2012 Apr 30. PMID: 22449005 , Jun-2012
Journal/Magazine covers	Grabham P, Bigelow A, Geard C. "Cover in International Journal of Radiation Biology included image from the PI's paper, '"DNA damage foci formation and decline in two-dimensional monolayers and in three-dimensional human vessel models: Differential effects according to radiation quality.' " International Journal of Radiation Biology. 2012 Jun;88(6):493-500. PMID: 22449005 , Jun-2012