Fiscal Year:	FY 2015	**Task Last Updated:**	FY 07/21/2015
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Project Title:	Combined Effects of Space Radiation and Microgravity on the Function of Human Capillaries and the Endothelial Barrier: Implications for Degenerative Disorders		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
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:**	13
Comments:			
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No. of Bachelor's Candidates:		**Monitoring Center:**	NASA ARC
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COI Name (Institution):	Sharma, Preety Ph.D. (Columbia University)		
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Task Description:	This proposal is aimed at determining the effects of space radiation combined with microgravity on the function of human blood vessels and capillaries. The average human body contains tens of thousands of miles of vessels that permeate every tissue down to the microscopic level; therefore, it is an important target for radiation and is also influenced by gravitational forces. The vascular system is crucial to healthy functioning of the tissues and its dysfunction is not only a primary event in a range of degenerative diseases but also an important influencing factor in many others. The two functions of the human vascular system that greatly affect human health and disease are, 1) angiogenesis - the growth of new vessels to replace damaged vessels, and 2) Barrier function – the process that allows nutritious molecules to cross from the blood to tissues and waste molecules to be cleared out from tissues. Disruption of these processes is known to cause degenerative disease. We have shown that space radiation inhibits angiogenesis and disrupts endothelial barrier function using human endothelial cells in 2 and 3-dimensional human tissue models. The doses and time course for radiation-induced events are now known which makes it possible to assay for joint effects with other environmental influences. Angiogenesis and barrier function are also affected by microgravity so there is a potential for further dysfunction of the human vasculature when applied in combination with radiation. Here, we propose a ground-based study using simulated microgravity to determine the combined effects of space radiation and microgravity on human blood vessel models and its impact on degeneration by testing for angiogenesis and endothelial barrier function using our established assays.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Tissue models The development of 3-Dimensional human tissue models from normal human cells and stem cells has great potential in many fields of medical research. Tissue models can more accurately depict human tissue since the cells can be arranged spatially as they would be in vivo and can interact with each other as they would in the human body. A neurovascular unit can be used for basic research on many aspects of the human brain. These include regeneration, synaptic function, and degeneration. Because the tissue model is derived from individual cells, each cell type can be altered genetically before it is incorporated into the model. The effects of radiation combined with simulated microgravity can be of benefit to the health of astronauts.
Task Progress:	Task progress The first opportunity to irradiate the vessel models was on the spring run at NASA Space Radiation Laboratory (NSRL) so initial experiments in the fall of 2014 were carried out on the effects of microgravity alone. It soon became clear that simulated microgravity has an effect on our vessel models. However, there were problems with the 3D clinostat running for long (more than 24 hours) periods. Further development of the clinostat out at our machine shop here at Columbia was necessary. During this time we carried out some experiments with single axis rotation (vertical and horizontal) as controls. It was found that for the effects on mature vessels, a vertical spin was sufficient to break down the structure of the vessel models. In contrast, studies on angiogenesis showed that even a horizontal spin was sufficient to alter development suggesting that turbulence may be an influencing factor. Further experiments in which we reduced the speed of rotation from 15 rpm to 5 rpm (resulting in much less turbulence in the culture flasks) showed that mature vessel structure was broken down even at lower speeds. These experiments indicate that removal of the vector of gravity is sufficient to cause an effect on mature vessels at least. These studies were not completed since the irradiations at NSRL Brookhaven started and it was necessary to carry out combined microgravity and radiation experiments. We expect to finish the studies on microgravity alone (comparing different spins axis directions with 3D rotation in developing and mature vessels) and fill in the gaps during the summer and fall after irradiations at NSRL (June 25th was our last irradiation). We did however, establish a protocol for the combined studies. Data showed that 5 rpm in a vertical spin was effective at breaking down the structure of mature vessels. We therefore used this protocol for experiments investigating both simulated microgravity and radiation. This protocol was used through the radiations in the spring and summer runs at NSRL. With an average of one run per week or so we have generated a significant amount of samples and data. Each experiment has fixed and stained samples that are imaged and then analyzed and the time of processing is significant. Therefore, there are a large amount of experiments still being processed (the last run was on June the 25th and at the time of writing this experiment is still running). We expect to process these samples and data over the next 2-3 months. Nevertheless, there is data so far that proves that simulated microgravity together with heavy ion radiation is at least additive in breaking down the structure of mature vessels. Thus, the adverse effects of radiation and simulated microgravity on angiogenesis and mature vessel integrity are distinct and are at least additive when applied together. Using a protocol in which the mature vessel cultures are rotated at 5 rpm in vertical spin together with a known effect of 75 cGy of 1 GeV Fe ions we investigated the effects of each, simulated microgravity and heavy ions. Vessels were grown at 1g until mature then irradiated with the chosen dose of Fe ions (75 cGy is sufficient to breakdown vessel morphology by approximately 50%). As expected 75 cGy caused the loss of full width vessels (12.5 microns diameter and larger) and an increase in vessels narrower than 12.5 microns in diameter suggesting that the heavy ions are causing collapse of vessels.. A 5 rpm vertical spin alone caused the loss of full width vessels and an increase in narrow vessels. The number of narrow vessels in fact increased in simulated microgravity indicating that the effect is distinct from that of heavy ions and further that in addition to degrading existing vessels it may be stimulating the extension narrow pioneering structures. Both together had a profound effect both full width vessels and narrow vessels. There was a distinct morphology when both agents are applied together. There are a number of vessels ending in dead ends and in fact very little tube structure left. In conclusion we have shown that simulated microgravity alone has little effect on the early motile tip stage of angiogenesis. In mature vessel models, simulated microgravity (rotation in the vertical plane only at 5 rpm) has a profound effect of reducing full width vessel models. Furthermore, together with heavy ions there is at least an additive effect of each agent.
Bibliography Type:	Description: (Last Updated: 03/04/2024)