Fiscal Year:	FY 2013	**Task Last Updated:**	FY 11/16/2012
PI Name:	Globus, Ruth Ph.D.		
Project Title:	Simulated Space Radiation and Weightlessness: Vascular-Bone Coupling Mechanisms to Preserve Skeletal Health		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Musculoskeletal Alterations Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Bone Fracture**:Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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PI Organization Type:	NASA CENTER	**Phone:**	650-604-5247
Organization Name:	NASA Ames Research Center		
PI Address 1:	Bone and Signaling Laboratory		
PI Address 2:	Space Biosciences Research Branch		
PI Web Page:			
City:	Moffett Field	**State:**	CA
Zip Code:	94035-1000	**Congressional District:**	18
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2010 Crew Health NNJ10ZSA003N
Start Date:	10/01/2011	**End Date:**	09/30/2015
No. of Post Docs:	3	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	7	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Alwood, Joshua (NASA Ames Research Center) Castillo, Alesha (Veterans Affairs Palo Alto Health Care System) Delp, Michael (University of Florida) Limoli, Charles (University of California, Irvine)		
Grant/Contract No.:	NCC 9-58-MA02501		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	(1) Original project aims/objectives. Long term spaceflight leads to extensive changes in the musculoskeletal system attributable to unloading in microgravity, although with future exploration outside the protection of Earth's magnetosphere space radiation also may have adverse, long term effects. Acute, whole body irradiation at high doses can cause significant depletion of stem/progenitor cell pools throughout the body as well as inflammation associated with prompt tissue degradation. To date, little is known about the combined effects of weightlessness and space radiation on the musculoskeletal system and its associated vasculature. Radiation can increase cancellous osteoclasts, leading to rapid bone loss, which can be mitigated in the short term by treatment with a potent anti-oxidant (a-lipoic acid). Furthermore, simulated weightlessness in adult mice exacerbates the adverse effects of space-relevant radiation on cancellous tissue, mechanical properties and osteoprogenitors, as well as long-term responses during recovery from disuse. If weightlessness undermines the capacity to mount radio-protective mechanisms, then potentially irreversible oxidative injury and persistent skeletal damage to stem and progenitor populations may ensue. Deficits in vascular-perfusion coupling also can lead to profound bone loss and may contribute to spaceflight-induced osteopenia. Together, these findings support a two-pronged approach for countermeasure development; one focusing on preventing acute bone loss and another on protecting cell populations needed for skeletal remodeling in the long term. Our long term goals are twofold; define the mechanisms and risk of bone loss in the spaceflight environment and facilitate the development of effective countermeasures if needed. Our working hypothesis is that prolonged musculoskeletal disuse and radiation together cause cumulative, adverse changes in the structure and function of bone and its vasculature resulting from oxidative stress, and prevent recovery from unloading by damaging the stem and progenitor cells needed for subsequent recovery. The rationale for this research is that a better understanding of the mechanisms and long-term risks posed by exposure to weightlessness and space radiation will improve the development and application of countermeasures for future exploration-class missions. (2) Key Findings. Progress has been made on multiple fronts during the first year of the grant. We have confirmed structural and cellular phenotypes with previous results. Work remains to study the cellular and molecular mechanisms in more detail and to investigate how antioxidants can effectively modulate skeletal radioresponses. The following provides a summary of key findings. Bone Structure and Vascular Reactivity Acute Effects • Radiation-induced bone loss results above a cumulative dose of 100 cGy from low- or high-LET ion constituents • Vasodilation responses to acetylcholine were diminished in gastrocnemius muscle feed arteries in hindlimb unloaded and irradiated mice relative to that in control animals. The combined effects of hindlimb unloading and irradiation did not further depress endothelium-dependent vasodilation. Simulated Spaceflight Effects on Osteoblast Cell Cultures • These results suggest that osteoprogenitor growth from marrow progenitors may be impaired above a threshold dose of heavy-ions between 20 and 50 cGy (3) These experiments inform the radiation doses and duration of hindlimb unloading to be utilized in future work, as part of Milestone 1, 2, and 3 of our grant proposal, and to establish treatment schedules to modulate bone structure and vascular reactivity (4) In the coming year, we plan to test antioxidant countermeasures to radiation-induced bone loss and to protect osteoprogenitors. Pilot studies will be conducted at ARC and NSRL/BNL to establish the efficacy of different antioxidant compounds and additional experiments will be conducted to investigate if simulated space-irradiation affects vascular reactivity, responses to unloading, and oxidative mechanisms.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research project focuses on the effects of spaceflight environmental factors, such as microgravity and irradiation, on the skeleton. Through use of an antioxidant as a potential countermeasure to the effects of spaceflight, our research could provide Earth-based benefits in areas including radioprotection, mitigation of oxidative stress and disuse osteoporosis.
Task Progress:	During this reporting period, we performed two series of experiments at the NASA Space Radiation Laboratory at Brookhaven, NSRL-BNL, (using iron (56Fe) or a sequential exposure to protons / iron / protons), and separate experiments at NASA Ames Research Center (ARC), (using 137Cs). Analysis of samples is still in progress from the recent NSRL experiments, which focused on acute effects of sequential radiation exposure in combination with disuse. Analysis of the experiment conducted at NASA ARC which focused on the acute effects of gamma irradiation and disuse on the vascular reactivity is nearing completion. The first series of experiments at NSRL/BNL and NASA ARC were conducted to identify the timing and extent of radiation and unloading effects on bone structure and function. Our results suggest unloading and irradiation affected skeletal structure of adult mice to a similar extent and the sequential beam exposure had similar effects as exposure to iron alone within a 2-week time frame. Vasodilation responses to acetylcholine were diminished in gastrocnemius muscle feed arteries in hindlimb unloaded and irradiated mice relative to controls. The combined effects of hindlimb unloading and irradiation did not further depress endothelium-dependent vasodilation. Results from separate, related experiments demonstrate that altered redox defense mechanisms and sensitivity to DNA-damage in osteoprogenitors and precursors persist long after acute exposure to heavy-ion irradiation. These results inform the radiation doses and duration of unloading to be utilized in future work, as part of Milestone 1, 2, and 3 of our grant proposal, and help establish treatment schedules to investigate the responses of bone structure and vascular reactivity to both radiation and simulated weightlessness. Thus, substantive progress has been made on multiple fronts during the first year of the grant. Work remains to study the cellular and molecular mechanisms in greater detail and to investigate how and which antioxidants effectively modulate skeletal changes in response to simulated spaceflight. ESTIMATED % COMPLETION PER AIM: AIM 1: ~75% complete AIM 2: ~10% complete. AIM 3: ~2% complete As outlined in our proposal, we have been actively involved with several Education & Outreach activities, including the STEM Teacher And Researcher (STAR), the Education Associates' Program (EAP) programs, and the Space Settlement Design Contest.

Bibliography Type:	Description: (Last Updated: 09/17/2021)
Abstracts for Journals and Proceedings	Alwood JS, Limoli CL, Delp MD, Castillo AB, Globus RK. "Simulated space radiation and weightlessness: vascular-bone coupling mechanisms to preserve skeletal health." 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
Abstracts for Journals and Proceedings	Globus RK, Alwood JS, Kumar A, Limoli CL. "Hypothesis: Space Radiation-Induced Bone Loss as Collateral Damage." 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