Fiscal Year:	FY 2016	**Task Last Updated:**	FY 03/10/2017
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:**	09/30/2016
No. of Post Docs:	5	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	1
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	3
No. of Bachelor's Candidates:	8	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 9/30/2016, per NSBRI (Ed., 8/26/15)		
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 (Florida State University) Limoli, Charles (University of California, Irvine)		
Grant/Contract No.:	NCC 9-58-MA02501		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Astronauts may develop bone loss in space as a result of environmental challenges such as exposure to weightlessness and ionizing radiation. Oxidative stress results from an imbalance between production of free radicals and the ability of cells to counteract their harmful effects at the molecular level. To date, little is known about the combined effects of weightlessness and space radiation on the musculoskeletal system, the cardiovascular system, and how these two systems interact in maintaining bone health. The overall objectives of our National Space Biomedical Research Institute (NSBRI)-supported research project were to define mechanisms and risks of bone loss in space, to explore the relationship between microvessel function and bone loss due to weightlessness and radiation exposure, and to help develop effective ways to prevent bone loss. Our NSBRI-supported research project can be considered quite productive--seven peer-reviewed primary papers have been published to date, one published review article, and numerous talks and posters were presented at national and international scientific conferences. Two of the published papers garnered considerable public interest and exposure in the popular press, while one was the subject of both a commentary and a recent article in JAMA. A new manuscript is now in review at a journal (Radiation Research). Three additional primary research papers acknowledging this grant's support are still in preparation (all experimental work complete), and a review article is also being prepared that integrates both our new findings over the life of this project and the contributions of others to this field of research. In the course of this project, two NASA postdoctoral fellowships (funded by the Space Biology program, 3-yr in duration) were awarded to perform work related to this grant. Further, results obtained in the course of executing this grant's research contributed key preliminary results to two new grants that were awarded recently by NASA. Thus, considerable scientific advances and leverage were realized as a consequence of this NSBRI award. Using mice to simulate weightlessness and space-relevant radiation, results from the series of studies supported by this grant demonstrate that both of these environmental conditions interact to induce early impairment of endothelium-dependent vasodilation and cancellous bone loss. However, the only sustained vascular endothelial cell dysfunction is that mediated by exposure to High-Z-High Energy ions (HZE) and not by simulated weightlessness. If such results translate to the human condition, then long-term dysfunction of the vascular endothelium induced by HZE particles could be a major contributor to the development of atherosclerotic cardiovascular disease in astronauts, as well as contribute to the long-term bone loss. We find that simulated weightlessness causes decrements in both slow-turnover cortical bone tissue and high turnover cancellous tissue, whereas ionization radiation (0.5-2Gy) causes decrements only in cancellous tissue. Whereas the radiation-induced deficits in skeletal microarchitecture diminish over a period of 6-7 months due to age-related bone loss in control animals, dysfunction in cell populations persists. HZE but not protons or gamma (<2Gy) cause defects in osteoblastogenesis from bone marrow derived stem cells and progenitors. This defect can be attributed to persistent deficits in progenitor cell proliferation and colony growth, whereas the capacity to differentiate into osteoblast-like cells and mineralize an extracellular matrix (the hallmark of osteoblasts) is retained. In addition, bones from HZE-irradiated animals can respond later to anabolic loading stimulus with improved bone formation, although there is some evidence from analyses by dynamic histomorphometry and gene expression that there may be persistent defects in osteoprogenitor cell populations localized to regions adjacent to the periosteal surfaces of bone tissue. Together, these findings on marrow-derived progenitors and periosteal cell behavior lead us to predict that fracture healing and perhaps other wound healing processes that depend mesenchymal stem cells derived from the marrow and/or periosteal bone surfaces are deficient after exposure to HZE at space relevant doses. This prediction is both consistent with a few reports in the scientific literature and may have relevance to regenerative medicine in space, thus represents a potentially important area for future study. With respect to prevention, either mechanical stimulation (resembling vigorous exercise) or feeding a diet containing dried plum, can improve bone structure despite prior exposure to HZE. In contrast, treatment with antioxidants that have displayed at least some radioprotective properties (lipoic acid injections, anti-oxidant cocktail, or treatment with an anti-inflammatory (Ibuprofen)) failed to prevent radiation-induced bone loss. These findings imply treatment with antioxidants alone are unlikely to prove fully protective to the skeleton exposed to ionizing radiation. In sum, findings from our studies show that in the short term, ionizing radiation and simulated weightlessness cause greater deficits in blood vessels when combined compared to either challenge alone. In the long term, HZE but not unloading, can lead to persistent, adverse consequences for bone cell and vessel function, possibly due to oxidative stress-related pathways. Novel countermeasures to radiation-induced damage to the skeleton identified in the course of this project include both mechanical stimulation and a dietary supplement.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	A better understanding of the mechanisms and long-term risks posed by exposure to weightlessness and radiation in space is needed to help protect the skeletal health of astronauts during and after long duration, exploration class missions. We hypothesize that countermeasures to unloading and radiation-induced bone loss that target cells responsible for bone formation and bone's vascular supply will be useful for limiting continued bone loss in space and preserving subsequent recovery. Cellular and molecular mechanisms that contribute to the formation of new bone (stem cells, osteoprogenitors, and osteoblasts) will be defined, using ground-based rodent models for simulating space radiation and weightlessness. On the basis of the mechanistic insight gained, potential anti-oxidant countermeasures will be tested in the following specific aims. Aim 1: Determine how prolonged weightlessness and space radiation (simulated spaceflight) cause functional and structural changes in skeletal vasculature and bone. Aim 2. Determine the extent to which specific countermeasures protect against weightlessness and space radiation-induced bone loss and vascular dysfunction. Aim 3. Determine how low dose space radiation influences later skeletal recovery from prolonged weightlessness. Aim 4. Determine if transient treatment with countermeasures protects from bone loss caused by weightlessness and radiation during subsequent aging. These studies will provide important new insight into the bone loss that is caused by musculoskeletal disuse and radiation at the molecular, cell, and tissue level, with biomedical applications to Earth (e.g., radiotherapy, accidental exposures), as well as space.
Task Progress:	Astronauts may develop bone loss in space as a result of environmental challenges, such as exposure to weightlessness and ionizing radiation. Oxidative stress results from an imbalance between production of free radicals and the ability of cells to counteract their harmful effects at the molecular level. The overall objectives of our research are to define the mechanisms and risks of bone loss in space and to help develop effective ways to prevent that bone loss. We hypothesize weightlessness and radiation together cause oxidative stress, adversely affecting both bone and the blood vessels that feed muscle and bone. This last year, four published papers describe results from our experiments with mice testing various aspects of our hypothesis. We examined the effects of radiation and/or simulated weightlessness by hindlimb unloading on bone and blood vessel function either after a short period or at a later time after transient exposures. In short term studies the combination of weightlessness and heavy ion radiation together cause worse deficits in blood vessel function than either factor alone, and these deficits appear to be mediated via free radical-related pathways. In contrast, long-term studies show that bones and vessels can recover from exposure to transient simulated weightlessness, but cannot recover fully from heavy ion radiation. With respect to prevention, either mechanical stimulation (resembling vigorous exercise) or feeding a diet containing dried plum, can improve bone structure despite prior exposure to heavy ion radiation. In sum, recent findings from our studies show that in the short term, ionizing radiation and simulated weightlessness cause greater deficits in blood vessels when combined compared to either challenge alone. In the long term, heavy ion radiation, but not unloading, can lead to persistent, adverse consequences for bone and vessel function, possibly due to oxidative stress-related pathways.
Bibliography Type:	Description: (Last Updated: 09/17/2021)
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