Fiscal Year:	FY 2010	**Task Last Updated:**	FY 09/15/2009
PI Name:	Bateman, Ted A. Ph.D.		
Project Title:	Space Radiation and Bone Loss: Lunar Outpost Mission Critical Scenarios and Countermeasures		
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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Zip Code:	27599	**Congressional District:**	4
Comments:	Previous affiliation was Clemson University; PI moved to UNC in fall 2010.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2007 NSBRI-RFA-07-01 Human Health in Space
Start Date:	10/01/2007	**End Date:**	09/30/2011
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	2	**No. of Master' Degrees:**	1
No. of Master's Candidates:	3	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Nelson, Gregory (Loma Linda University)		
Grant/Contract No.:	NCC 9-58-BL01302		
Performance Goal No.:			
Performance Goal Text:			
	Crews on exploratory missions will face complex radiation from cosmic and solar sources with components ranging from protons to iron. We have identified trabecular bone loss in mice after exposure to multiple radiation types with doses ranging from 0.5 Gy to 2 Gy, suggesting space radiation may increase bone loss from reduced gravity during exploratory missions. The bone loss is rapid and initiated by an early activation of osteoclasts. The impact of radiation on bone quality and fracture healing in reduced gravity is unknown, and must be studied to understand effects of space radiation on bone health. The long-term objective of the proposed research is the development of countermeasures to prevent bone loss during missions and thus reduce fracture risk. To define the risks associated with space radiation-induced bone loss, the proposed aims will examine effects of		

Task Description:	modeled space radiation using scenarios applicable for Lunar Outpost missions: Specific Aim 1: Examine the combined effects of a modeled solar particle event and unloading on bone, and subsequent recovery during reloading. Hypothesis: Proton radiation with unloading will induce a more severe bone loss than unloading alone. Specific Aim 2: Examine the cellular and molecular mechanisms for initiating bone loss following exposure to several types of modeled space radiation, including acute proton exposure, low-dose-rate proton exposure, and mixed radiation types (proton and HZE). Understanding underlying molecular causes is critical to developing countermeasures for radiation-induced bone loss. Hypothesis: The initiating mechanism of bone loss is initiated by osteoclast activation caused by a radiation-induced inflammatory response. Specific Aim 3: Test the efficacy of three countermeasures for bone loss caused by proton exposure: 1) the bisphosphonate risedronate; 2) the RANKL blocking protein osteoprotegerin, and 3) an antioxidant agent, alpha-lipoic acid. Hypothesis: Potent inhibitors of bone resorption, both zoledronate and osteoprotegerin will prevent the bone loss caused by radiation. Antioxidants will address multiple radiation-induced problems; alpha-lipoic acid decreases osteoclast differentiation and activity.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Bone atrophy and increased risk of bone fracture are consequences of exposure to radiation for cancer treatment. Osteopenia and osteoporosis have been characterized as pathological conditions following therapeutic irradiation. There is an increased incidence of spontaneous hip fractures demonstrated by patients receiving radiation to treat pelvic cancers. Postmenopausal women receiving radiotherapy to treat cervical, rectal and anal cancers have an increased hip fracture risk of 60-200% (Baxter et al., JAMA 2005). Morbidity and mortality statistics for hip fractures in this population are poor: nearly one in four will not survive a year after fracture and a significant majority of survivors will never return quality of life to pre-fracture abilities. As long-term survivorship increases with improved diagnosis and treatment, the morbidity and mortality associated with osteoporosis and hip fractures within this population is becoming a significant concern. This loss of bone mass following radiotherapy has been hypothesized to occur as a result of damage to bone-forming osteoblasts and the bone vasculature itself. While previous studies typically observed atrophy as a late effect, loss of volumetric bone mineral content has been reported in cervical cancer patients five weeks post treatment and described as a low-turnover type of osteoporosis. An inhibition of osteoblasts and osteoblast progenitors from radiation exposure has been further described both in vitro and in vivo, and we have reported a long-term reduction of bone mass in irradiated mice. Despite evidence that bone loss can occur soon after irradiation, a putative increase in osteoclast activity has received little attention as a potential contributor to radiation-induced osteoporosis. To date, pharmacological interventions to prevent bone loss caused by radiation therapy have not been employed. In fact, no animal model currently exists to identify causal mechanisms and to properly develop such therapies. Our work through the last year has identified a rapid activation of osteoclasts after radiation exposure that is prevented by treatment with risedronate. The following aims supported by NSBRI have direct clinical relevance. Specific Aim 2a: Radiation exposure results in an early activation of osteoclasts leading to rapid bone loss (Willey et al., Radiation Res, 2008). Specific Aim 3: Risedronate prevents radiation-induced bone loss (Willey et al., Bone, in press). Clinical Trials: Radiation therapy (RT) to treat cervical and lung cancers cause a decline in proximal femur strength and thoracic lumbar vertebra bone mineral density, respectively. Procter and Gamble Pharmaceuticals awarded us an unrestricted grant to study bone loss in cervical cancer patients (PI Dr. Joyce Keyak University of California at Irvine). A finite element model of the proximal femur was developed from CT imaging taken on the last day of RT (6 weeks after starting RT) and compared to the pretreatment planning CT scan. FEA tests the strength of the femur when single-leg stance and falling loads are applied. Of the four patients studied to date, there is a significant decline in single leg stance load ($p = 0.04$) and a trend towards a decline in fall load ($p = 0.11$). Dr. Larry Marks (Chair, Dept. of Radiation Oncology, UNC Chapel Hill) has thoracic CT scans from approximately 100 lung cancer patients before and six months after RT. The goal of the original prospective study was to examine the development of lung fibrosis. The body of 6 thoracic vertebrae from 15 of these patients have been analyzed. On average, the patients lost -21% vBMD in these six vertebrae. For women, there is a significant correlation with the degree of vBMD decline and age, with greater loss occurring with increasing age ($p = 0.03$). A similar trend was observed among men ($p = 0.07$).
Task Progress:	Crews on exploratory missions will face complex radiation from cosmic and solar sources with components ranging from protons to iron. We have identified trabecular bone loss in mice after exposure to multiple radiation types with doses ranging from 0.5 Gy to 2 Gy, suggesting space radiation may increase bone loss from reduced gravity during exploratory missions. The bone loss is rapid and initiated by an early activation of bone resorbing cells. The impact of radiation on bone quality in reduced gravity is unknown, and must be studied to understand effects of space radiation on bone health. The long-term objective of the proposed research is the development of countermeasures to prevent bone loss during missions and thus reduce fracture risk. The second year of this project was very productive, with progress made on all three Aims. Specific Aim 1: Bone loss from exposure to a 1 Gy whole-body dose of protons and skeletal loading is additive. Manuscript in preparation. Specific Aim 2b: Exposure to a dose of <50 cGy radiation of mixed type results in both cortical and trabecular bone loss. Paper published July 2008.

	Specific Aim 2c: Bone loss from exposure to ionizing radiation is a local response and is preceded by greater expression on proinflammatory cytokines. Specific Aim 3a: Risedronate prevents radiation-induced bone loss. Publication in press for the journal Bone. Specific Aim 3b: Ongoing tests of IL-1 receptor antagonist, TNF binding protein and ascorbic acid (vitamin C) as countermeasures to block local 1) radiation mediated inflammation, and 2) reactive oxygen species created by ionizing radiation and resulting cell death.
Bibliography Type:	Description: (Last Updated: 11/12/2020)
Articles in Peer-reviewed Journals	Allen DL, Bandstra ER, Harrison BC, Thorng S, Stodieck LS, Kostenuik PJ, Morony S, Lacey DL, Hammond TG, Leinwand LL, Argraves WS, Bateman TA, Barth JL. "Effects of spaceflight on murine skeletal muscle gene expression." J Appl Physiol. 2009 Feb;106(2):582-95. PubMed PMID: 19074574 , Feb-2009
Articles in Peer-reviewed Journals	Bandstra ER, Thompson RW, Nelson GA, Willey JS, Judex S, Cairns MA, Benton ER, Vazquez ME, Carson JA, Bateman TA. "Musculoskeletal changes in mice from 20-50 cGy of simulated galactic cosmic rays." Radiation Research, 2009 Jul;172(1):21-9. PubMed PMID: 19580504 , Jul-2009
Articles in Peer-reviewed Journals	Lloyd SA, Yuan YY, Simske SJ, Riffle SE, Ferguson VL, Bateman TA. "Administration of high-dose macrophage colony-stimulating factor increases bone turnover and trabecular volume fraction." J Bone Miner Metab. 2009 Sep;27(5):546-54. Epub 2009 Mar 27. PubMed PMID: 19326045 , Sep-2009
Articles in Peer-reviewed Journals	Lloyd SA, J, Bandstra ER, Travis ND, Nelson GA, Bourland JD, Pecaut MJ, Gridley DS, Willey JS, Bateman TA. "Spaceflight-relevant types of ionizing radiation and cortical bone: Potential LET effect?" Advances in Space Research. 2008 Dec 15;42(12):1889-97. PMID: 19122806 , http://dx.doi.org/10.1016/j.asr.2008.08.006 , Dec-2008
Articles in Peer-reviewed Journals	Willey JS, Livingston EW, Robbins ME, Bourland JD, Tirado-Lee L, Smith-Sielicki H, Bateman TA. "Risedronate prevents early radiation-induced osteoporosis in mice at multiple skeletal locations." Bone. 2009 Sep 8. [Epub ahead of print] PubMed PMID: 19747571 , Sep-2009
Awards	Lemus M. "Exceptional Research Opportunities Program from the Howard Hughes Medical Institute, Summer 2009." May-2009
Awards	Tirado L. "Travel Award from Society for Advancement of Chicanos and Native Americans in Science (SACNAS) for the International Polar Year: Global Change in Our Communities Conference, Salt Lake City, Utah, October 09-12, 2008." Oct-2008
Patents	N/A. Application submitted. Patent Application, February 2008. Feb-2008 Bateman TA, Willey JS. "Use of antiresorptive compounds to prevent radiation-induced activation of osteoclasts and resulting bone loss."