Fiscal Year:	FY 2011	**Task Last Updated:**	FY 01/11/2011
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		
PI Email:	bateman@unc.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	720-810-3626
Organization Name:	University of North Carolina at Chapel Hill		
PI Address 1:	152 MacNider Hall, CB 7575		
PI Address 2:	Dept of Biomedical Engineering		
PI Web Page:			
City:	Chapel Hill	**State:**	NC
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:**	3
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**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 0.3 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 modeled space radiation using scenarios applicable for Lunar Outpost missions:

Task Description:

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:

We have completed a clinical trial at the University of California - Irvine in collaboration with Drs. Keyak, Lang, and Carpenter. We show that women receiving radiation therapy for treatment of gynecological tumors lose bone mass at an extraordinary rate: during the six weeks of radiation therapy, on average women lose as much bone as a women will during the two years immediately after menopause. Dr. Bateman has also scored very well (7th percentile) on an NIH grant to study the preclinical aspects of bone loss in women with gynecological tumors receiving radiation therapy. Study Summary:

Postmenopausal women receiving radiation therapy (RT) for pelvic tumors have a 65-200% increased risk of hip fracture compared to women receiving non-RT cancer treatment. It is generally accepted that RT damages local osteoblasts and vasculature resulting in a low turnover, gradual decline in bone mass. However, it has recently been observed in rodent models that ionizing radiation activates osteoclasts. To test the hypothesis that early osteoclastic resorption may cause a rapid loss of bone, changes in proximal femur strength, bone density, and mineral content were examined in women receiving RT for gynecological tumors.

Eight women (age 36-71 years) with cervical (n=6), vaginal, or uterine cancer provided informed consent. CT scans were performed pre-RT and on the last day of RT (6 weeks later). Patients received 50.4 Gy over the course of 28 days. Total dose to the proximal femur was ~25.0 Gy. CT scans were used for finite element strength and volumetric quantitative CT (vQCT) analyses. Proximal femur strength was calculated for models representing a single-limb stance load (SL) and a fall load (FL) onto the posterolateral aspect of the greater trochanter. Volumetric bone mineral density (vBMD) and bone mineral content (BMC) were calculated via vQCT for trabecular (Tr), cortical (Co) and integral (Tr + Co) compartments of the proximal femur. Significance was determined by paired t-test. All patients lost proximal femur strength for both SL and FL conditions (-5%,-10% $p<0.05$). vBMD was reduced in both the Tr and integral (-17%,-6% $p<0.01$), but not the Co, compartments. BMC was reduced for all regions: Tr -24%, Co -14% and integral -16% ($p<0.02$). Co BMC decline is accompanied by a loss of Co, and integral volume (-14%,-10% $p<0.05$) indicating periosteal resorption and a thinning of the cortex. Linear regression analysis shows a greater loss of Tr BMC with decreasing age ($p=0.03$), but there was no correlation of age with BMD or strength changes.

RT caused rapid decline of bone strength, density and mineral content in the proximal femur. Only an early activation of osteoclasts can account for this rate of loss (BMC decline >2%/wk). For context, the bone loss from 6-wks of RT is roughly equivalent to 3 years of bone loss in women due to menopause. Future studies will examine later time points to determine the degree of recovery. As more data are available, prophylactic treatment of radiation-induced bone loss with antiresorptives should be considered.

Task Progress:

Bisphosphonate Countermeasures: One of our accomplishments for the year include continuing with countermeasure development by improving bisphosphonate therapy. In early 2010 we published a paper (Willey et al., Bone 2009) showing that risedronate (a relatively high dose) effectively prevents bone loss from a 2 Gy whole body dose of X-rays. Because NASA is currently testing alendronate and zoledronate in astronauts on the International Space Station, we are testing these bisphosphonates for their ability to prevent space radiation-induced osteoporosis. We have tested a single dose of 5 ug/kg zoledronate to prevent bone loss from 2 Gy of X-rays. 5 ug/kg was chosen because it effectively prevents bone destruction in mice with breast and prostate cancer bone metastases. We also tested a single supra-clinical dose of 50 ug/kg. Compared to placebo treated control mice, 5 ug/kg did not effectively prevent bone loss, and 50 ug/kg prevented ~half of the bone loss. We are in the process of testing more frequent dosing (1-3 ug/kg/day).
Antioxidant Countermeasures: Oxidative stress after irradiation has been speculated to mediate radiation-induced bone loss, as some evidence points to the efficacy of a-lipoic acid. Antioxidants, including alipoic acid, have been effective in preventing bone loss in models of reduced-estrogen induced osteoporosis. We have tested the efficacy of high doses of two antioxidants in terms of preventing bone loss after irradiation (a-lipoic acid and ascorbic acid): Neither suppressed any functional bone loss.

Predisposition of Heredity: We have also performed an experiment comparing the response of 4 strains of mice to radiation-induced bone loss, with the goal of determining both improving our spaceflight model and determining if there is a hereditary/genotype predisposition to being radiation sensitive or in sensitive. We want to explore transitioning our model towards using a higher bone density strain of mouse. When combining radiation with another skeletal challenge, such as disuse, the low bone density C57BL/6 (B6) mice have very little bone remaining. BALBc mice do respond the same as B6 mice; the rate and degree of bone loss from irradiation are the same. We are in the process of analyzing data from two other strains: DBA mice are considered to be radiation resistant and C3H mice are less susceptible to disuse osteoporosis. We are potentially observing some preservation of bone moss in DBA and C3H mice, however more analysis is necessary.

Rotating wall vessel changes in osteoclast gene expression profile: We collaborated with Dr. Reddy at the Medical University of South Carolina on a project examining changes in gene expression profile in osteoclast cultures using the rotating wall vessel to model microgravity (Sambandam et al., J Cell Biochem 2010).

Bibliography Type:	Description: (Last Updated: 11/12/2020)
Abstracts for Journals and Proceedings	Lawrence M, Willey J, Saynak M, Bateman T, Marks L. "Radiation Therapy Causes a Rapid Loss of Bone Mineral Density of Thoracic Vertebra in Women and Men Lung Cancer Patients." 2010 ASBMR Annual Meeting, Toronto, Canada, October 15-19, 2010. J Bone Miner Res 2010;25 (Suppl 1). Available at http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=b8337276-1e33-40fd-868d-020591d48589 Accessed January 11, 2011. , Oct-2010
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