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 Outp	post Mission Critical Sce	enarios and Countermeasures
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline Element/Subdiscipline:	NSBRIMusculoskeletal Alterations Team		
Joint Agency Name:	TechPort:		No
Human Research Program Elements:	(1) HHC :Human Health Countermeasures		
Human Research Program Risks:	 Bone Fracture: Risk of Bone Fracture d Osteo: Risk Of Early Onset Osteoporosis 	ue to Spaceflight-induce Due To Spaceflight	d Changes to Bone
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	Previous affiliation was Clemson University	; PI moved to UNC in fa	all 2010.
Project Type:	Ground Solicita	tion / 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 N	o. 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 con from protons to iron. We have identified tra doses ranging from 0.3 Gy to 2 Gy, suggest exploratory missions. The bone loss is rapid The impact of radiation on bone quality and understand effects of space radiation on bon development of countermeasures to prevent To define the risks associated with space rad	nplex radiation from cos becular bone loss in mice ing space radiation may and initiated by an early fracture healing in reduc the health. The long-term bone loss during mission diation-induced bone loss	mic and solar sources with components ranging e after exposure to multiple radiation types with increase bone loss from reduced gravity during v activation of osteoclasts. ced gravity is unknown, and must be studied to objective of the proposed research is the ns and thus reduce fracture risk. s, the proposed aims will examine effects of modeled
	space radiation using scenarios applicable for	or Lunar Outpost mission	15:

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 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) on the posterolateral aspect of the greater trochanter. All patients lost proximal femur; Significance was determined by paired t-test. All patients lost proximal femur strength for by points of the proximal femur; Significance was determined by paired t-test. All patients lost proximal femur; Significance was determined by 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
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 eloss, 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 C57BL/6 (B6) mice have very little bone remaining. BALBc mice do respon

Bibliography Type:	Description: (Last Updated: 11/12/2020)
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Abstracts for Journals and Proceedings	Lloyd S, Ferguson V, Simske S, Dunlap A, Livingston E, Bateman T. "Effects of Animal Enclosure Module Spaceflight Hardware on the Skeletal Properties of Ground Control Mice." 2010 ASBMR Annual Meeting, Toronto, Canada, October 15-19, 2010. J Bone Miner Res 2010;25 (Suppl 1). Available at <u>http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=cfd9d910-f993-46b5-aca0-fb864b900ec2</u> Accessed January 11, 2011. , Oct-2010
Abstracts for Journals and Proceedings	Bateman TA, Lang TL, Carpenter RD, Lawrence MV, Sehgal V, Ramsinghani NS, Kuo JV, Al-Ghazi M, Willey JS, Keyak JH. "Radiation Therapy Causes Rapid Loss of Proximal Femur Bone Strength and Density in Women with Gynecological Tumors." American Society for Radiation Oncology 52nd Annual Meeting, San Diego, CA, October 31-November 4, 2010. International Journal of Radiation Oncology*Biology*Physics. 2010 Nov 1;78(3 Suppl):S597. http://dx.doi.org/10.1016/j.ijrobp.2010.07.1391, Nov-2010
Abstracts for Journals and Proceedings	Bateman TA, Lang TL, Carpenter RD, Lawrence MV, Sehgal V, Ramsinghani NS, Kuo JV, Al-Ghazi M, Willey JS, Keyak JH. "Radiation Therapy Causes Rapid Loss of Proximal Femur Bone Strength and Density in Women with Gynecological Tumors." 2010 ASBMR Annual Meeting, Toronto, Canada, October 15-19, 2010. J Bone Miner Res 2010 25(Suppl 1). <u>http://www.asbmr.org/Meetings/AnnualMeeting/AbstractDetail.aspx?aid=900fc549-8d96-4996-b24c-548993cb868c</u> Accessed January 11, 2011. , Oct-2010
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. 2010 Jan;46(1):101-11. Epub 2009 Sep 9. PMID: 19747571, Jan-2010