Fiscal Year:	FY 2009	**Task Last Updated:**	FY 11/05/2008
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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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:**	2
No. of PhD Candidates:	3	**No. of Master' Degrees:**	1
No. of Master's Candidates:	3	**No. of Bachelor's Degrees:**	4
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):	Nelson, Gregory (Loma Linda University)		
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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:

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, with incidents generally being documented one to five years after therapy. 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.

The effect of radiation on the number and activity of osteoclasts is varied in published reports, from observed decreases in osteoclast numbers, to stable numbers, to a qualitative description of an increase in the osteoclast population. A better understanding of the effects of radiation on osteoclasts needs to be addressed in order to reduce or prevent the subsequent bone atrophy and fracture risk.

Research Impact/Earth Benefits:

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.

Female C57BL/6 mice were exposed to a 2 Gy whole-body dose of x-rays, or not irradiated. A serum marker for osteoclast activity (TRAP5b) was significantly increased 1 and 3 days after exposure (50% and 14%, respectively). Histological examination of bones collect from mice 3 days after exposure revealed a significant increase osteoclast number and surface. There were no changes in serum osteocalcin (a marker for osteoblast activity) or osteoblast surface.

Specific Aim 3: Risedronate prevents radiation-induced bone loss.

Twenty-week-old female C57BL/6 mice were exposed to a 2 Gy whole-body dose of x-rays, or not irradiated. Groups (3 groups) included non-irradiated controls administered a placebo injection, irradiated mice administered a placebo injection, and irradiated mice treated with risedronate (30 ug/kg every other day. Within these three groups mice were humanely euthanized at 1, 2, and 3 weeks after exposure. There was significant bone loss of trabecular bone at three skeletal sites (proximal tibia, distal femur, and 5th lumbar spine) at 1 weeks after exposure. Risedronate prevented this bone loss entirely.

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 first year of this project was very productive, with progress made on all three Aims.

Aim 1: Bone loss from exposure to a 1 Gy whole-body dose of protons and skeletal loading is additive.

Mice were exposed to a 1 Gy dose or protons and hindlimb suspended, a model for skeletal unloading, for a duration of 4-weeks (mimicking long-term spaceflight). Despite a profound bone loss from unloading, mice exposed to both unloading and protons had significantly more bone loss than unloaded mice not exposed to radiation.

Aim 2a: Radiation exposure results in an early activation of osteoclasts leading to rapid bone loss.

Task Progress:	Mice were exposed to a 2 Gy dose of x-rays, or not irradiated. A serum marker for osteoclast activity (TRAP5b) was significantly increased 1 and 3 days after exposure. Histological examination of bones collect from mice 3 days after exposure revealed a significant increase osteoclast number and surface. There were no changes in serum osteocalcin (a marker for bone formation) or osteoblast surface. Aim 2b: Exposure to a dose of <50 cGy radiation of mixed type results in both cortical and trabecular bone loss. Bones were collected from a study in which mouse brains were exposed to collimated iron radiation. These conditions resulted in exposure to a complex mixtures of charged particles transmitted by the collimator. Measured radiation doses of uncollimated secondary particles were 0.47 Gy at the proximal humerus. The proximal humerus of irradiated mice had lower trabecular bone volume fraction, lower trabecular thickness, greater cortical porosity, and lower polar moment of inertia. Aim 3: Risedronate prevents radiation-induced bone loss. Mice were exposed to a 2 Gy dose of x-rays, or not irradiated. Groups (3) included non-irradiated controls administered a placebo injection, irradiated mice administered a placebo injection, and irradiated mice treated with risedronate (30 ug/kg every other day). Within these three groups mice were humanely euthanized at 1, 2, and 3 weeks after exposure. There was significant bone loss of trabecular bone at three skeletal sites (proximal tibia, distal femur, and 5th lumbar spine) 1 week after exposure. Risedronate prevented this bone loss entirely.
Bibliography Type:	Description: (Last Updated: 11/12/2020)
Abstracts for Journals and Proceedings	Bowman LS, Livingston EW, Willey JS, Robbins ME, Bourland JD, Bateman TA. "Radiation-induced bone loss: description of dose, time course, age, strain and sex variables." American Society for Bone and Mineral Research 30th Annual Meeting, Montreal, Canada, Sept. 12-16, 2008. American Society for Bone and Mineral Research, Abstract Book, September 2008. , Sep-2008
Abstracts for Journals and Proceedings	Willey JS, Livingston EW, Bowman LC, Robbins ME, Bourland JD, Bateman TA. "Risedronate prevents early radiation-induced bone loss at multiple skeletal sites." American Society for Bone and Mineral Research 30th Annual Meeting, Montreal, Canada, Sept. 12-16, 2008. American Society for Bone and Mineral Research, Abstract Book, September 2008. , Sep-2008
Abstracts for Journals and Proceedings	Bandstra ER, Riffle SE, Lloyd SA, Willey JS, Nelson GA, Pecaut MJ, Bateman TA. "Combined effect of irradiation and unloading on murine bone." American Society for Bone and Mineral Research 30th Annual Meeting, Montreal, Canada, Sept. 12-16, 2008. American Society for Bone and Mineral Research, Abstract Book, September 2008. , Sep-2008
Abstracts for Journals and Proceedings	Willey JW, Livingston EW, Bowman LC, Robbins ME, Bourland JD, Bateman TA. "The antiresorptive agent risedronate prevents early radiation-induced bone loss." 2008 Radiation Research Society 54th Annual Meeting, Boston, MA, Sept 20-24, 2008. Radiation Research Society, Abstract Book, September 2008. , Sep-2008
Abstracts for Journals and Proceedings	Willey JS, Gridley DS, Pecaut MJ, Norrdin RW, Bateman TA. "An acute 7 gray dose of gamma-radiation induces a profound and rapid loss of trabecular bone in mice." American Society for Bone and Mineral Research 29th Annual Meeting, Honolulu, HI, Sept. 16-19, 2007. American Society for Bone and Mineral Research 29th Annual Meeting, Honolulu, HI, Sept. 16-19, 2007. Abstract Book, September 2007. , Sep-2007
Abstracts for Journals and Proceedings	Lloyd SA, Bateman TA. "Disuse exacerbates suppression of bone formation with administration of low-dose antiresorptive drugs." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):18. , Oct-2008
Abstracts for Journals and Proceedings	Bandstra ER, Pecaut MJ, Anderson ER, Willey JS, De Carlo F, Stock SR, Gridley DS, Nelson GA, Bateman TA. "Bone loss following proton irradiation." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):16. , Oct-2007
Abstracts for Journals and Proceedings	Livingston EW, Bateman TA. "Long-term effects of heavy ion radiation on bone loss in mice." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):18. , Oct-2007
Abstracts for Journals and Proceedings	Smith LC, Bateman TA. "Effect of low-energy x-rays on trabecular bone loss in mice." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):9. , Oct-2007
Abstracts for Journals and Proceedings	Tirado L, Willey JS, Bateman TA. "Effect of low dose ionizing radiation on bone metabolism in rats." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):13. , Oct-2007
Abstracts for Journals and Proceedings	Riffle S, Yuan YY Bateman TA. "Macrophage colony stimulating factor produces increased trabecular bone density and turnover, characteristic of an anabolic agent." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):13. , Oct-2007
Abstracts for Journals and Proceedings	Anderson ER, Willey JS, Nagatoni J, Bateman TA. "Examining the early response of osteoclasts to ionizing radiation." American Society for Gravitational and Space Biology 23rd Annual Meeting, Moffett Field, CA, October 25-28, 2007. Gravitational and Space Biology 2007 Oct;21(1):4. , Oct-2007

Articles in Peer-reviewed Journals	Yuan YY, Kostenuik PJ, Ominsky MS, Morony S, Adamu S, Simionescu DT, Basalyga DM, Asuncion FJ, Bateman TA. "Skeletal deterioration induced by RANKL infusion: a model for high-turnover bone disease." Osteoporos Int. 2008 May;19(5):625-35. PMID: 18038244 , May-2008
Articles in Peer-reviewed Journals	Allen DL, Bandstra ER, Harrison BC, Thorng S, Stodieck LS, Kosteniuk 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. Submitted, 2008. , Sep-2008
Articles in Peer-reviewed Journals	Bandstra ER, Pecaut MJ, Anderson ER, Willey JS, De Carlo F, Stock SR, Gridley DS, Nelson GA, Levine HG, Bateman TA. "Long-term dose response of trabecular bone in mice to proton radiation." Radiat Res. 2008 Jun;169(6):607-14. PMID: 18494551 , Jun-2008
Articles in Peer-reviewed Journals	Bandstra ER, Thompson RW, Nelson GA, Judex S, Cairns MA, Benton ER, Willey JS, Vazquez ME, Carson JA, Bateman TA. "Bone and muscle changes in skeletally mature mice in response to modeled galactic cosmic rays." Radiat Res. Submitted, 2008. , Sep-2008
Articles in Peer-reviewed Journals	Gridley DS, Obenaus A, Bateman TA, Pecaut MJ. "Long-term changes in rat hematopoietic and other physiological systems after high-energy iron ion irradiation." Int J Radiat Biol. 2008 Jul;84(7):549-59. PMID: 18661371 , Jul-2008
Articles in Peer-reviewed Journals	Lloyd SA, Travis ND, Lu T, Bateman TA. "Development of a low-dose anti-resorptive drug regimen reveals synergistic suppression of bone formation when coupled with disuse." J Appl Physiol. 2008 Mar;104(3):729-38. PMID: 18174391 , Mar-2008
Articles in Peer-reviewed Journals	Lloyd SA, Yuan YY, Kostenuik PJ, Ominsky MS, Lau AG, Morony S, Stolina M, Asuncion FJ, Bateman TA. "Soluble RANKL induces high bone turnover and decreases bone volume, density, and strength in mice." Calcif Tissue Int. 2008 May;82(5):361-72. PMID: 18465074 , May-2008
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. Submitted, 2008. , Sep-2008
Articles in Peer-reviewed Journals	Willey JS, Grilly LG, Howard SH, Pecaut MJ, Obenaus A, Gridley DS, Nelson GA, Bateman TA. "Bone architectural and structural properties after 56Fe26+ radiation-induced changes in body mass." Radiat Res. 2008 Aug;170(2):201-7. PMID: 18666808 , Aug-2008
Articles in Peer-reviewed Journals	Willey JS, Lloyd SA, Robbins ME, Bourland JD, Smith-Sielicki H, Bowman LC, Norrdin RW, Bateman TA. "Early increase in osteoclast number in mice following whole-body irradiation with 2 Gy X-rays." Radiat Res. 2008 Sep;170(3):388-92. PMID: 18763868 , Sep-2008
Awards	Riffle S. "2008 ACC Undergraduate Research Conference (one of ten Clemson representatives), Florida State University, Tallahassee, Florida, April 19, 2008." Apr-2008
Awards	Tirado L. "2008 ACC Undergraduate Research Conference (one of ten Clemson representatives), Florida State University, Tallahassee, Florida, April 19, 2008." Apr-2008
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, July 2008." Jul-2008
Awards	Lemus M. "Undergraduate Research Fellowship from the South Carolina Space Grant Consortium, April 2008." Apr-2008
Awards	Bateman TA. "Thora W. Halstead Young Investigator's Award, American Society for Gravitational and Space Biology (ASGSB), October 2007." Oct-2007
Awards	Anderson E. "Best Undergraduate Research Presentation and Travel Awards from the American Society for Gravitational and Space Biology, October 2007." Oct-2007
Awards	Willey J. "Post-doctoral Fellowship from the National Space Biomedical Research Institute, October 2007." Oct-2007
Awards	Bowman L. "Graduate Student Research Program Fellowship from the South Carolina Space Grant Consortium, April 2008." Apr-2008
Books/Book Chapters	Bateman TA, Bandstra ER, Willey JS, Lloyd SA, Yuan YY, Bourne J. "How animal models inform the debate." in "Bone loss during spaceflight : etiology, countermeasures, and implications for bone health on Earth." Ed. P.R. Cavanagh, A.J. Rice. Cleveland : Cleveland Clinic Press, c2007. p. 189-199., Dec-2007
Papers from Meeting Proceedings	Bandstra ER, Judex S, Vazquez ME, Bateman TA. "Murine bone loss following local irradiation." 29th Annual Meeting of the American Society for Bone and Mineral Research, Honolulu, HI, September 16-19, 2007. 29th Annual Meeting of the American Society for Bone and Mineral Research, Abstract Book, September 2007. , Sep-2007