

<b>Fiscal Year:</b>	FY 2012	<b>Task Last Updated:</b>	FY 04/04/2013
<b>PI Name:</b>	Bloomfield, Susan A. Ph.D.		
<b>Project Title:</b>	Maintaining Musculoskeletal Health in the Lunar Environment		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	NSBRI		
<b>Program/Discipline--Element/Subdiscipline:</b>	NSBRI--Musculoskeletal Alterations Team		
<b>Joint Agency Name:</b>	<b>TechPort:</b>	No	
<b>Human Research Program Elements:</b>	(1) <b>HHC:</b> Human Health Countermeasures		
<b>Human Research Program Risks:</b>	(1) <b>Bone Fracture:</b> Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) <b>Osteo:</b> Risk Of Early Onset Osteoporosis Due To Spaceflight		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
<b>PI Email:</b>	<a href="mailto:sbloom@tamu.edu">sbloom@tamu.edu</a>	<b>Fax:</b>	FY 979-862-1692
<b>PI Organization Type:</b>	UNIVERSITY	<b>Phone:</b>	979-845-2871
<b>Organization Name:</b>	Texas A&M University		
<b>PI Address 1:</b>	Department of Health & Kinesiology		
<b>PI Address 2:</b>	400 Harvey Mitchell Pkwy, Suite 300		
<b>PI Web Page:</b>			
<b>City:</b>	College Station	<b>State:</b>	TX
<b>Zip Code:</b>	77843-4375	<b>Congressional District:</b>	17
<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2007 Crew Health NNJ07ZSA002N
<b>Start Date:</b>	06/01/2008	<b>End Date:</b>	09/30/2012
<b>No. of Post Docs:</b>	0	<b>No. of PhD Degrees:</b>	0
<b>No. of PhD Candidates:</b>	2	<b>No. of Master' Degrees:</b>	1
<b>No. of Master's Candidates:</b>	3	<b>No. of Bachelor's Degrees:</b>	0
<b>No. of Bachelor's Candidates:</b>	2	<b>Monitoring Center:</b>	NSBRI
<b>Contact Monitor:</b>	<b>Contact Phone:</b>		
<b>Contact Email:</b>			
<b>Flight Program:</b>			
<b>Flight Assignment:</b>	NOTE: End date change to 9/30/2012 (from 5/31/2012) per NSBRI (Ed., 1/24/2012)		
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Braby, Leslie ( Texas Engineering Experiment Station ) Hogan, Harry ( Texas A&M University ) Fluckey, James ( Texas A&M University ) Wang, Suojin ( Texas A&M University )		
<b>Grant/Contract No.:</b>	NCC 9-58-MA01602		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

## Task Description:

The over-arching goal of this project is to determine if the usual bone and muscle loss observed during planetary missions will be exacerbated by exposure to space radiation. Using the partial g mouse model originally developed at MIT/Harvard by Drs. Wagner and Bouxsein (the partial g mouse), we first performed experiments to verify whether the partial loading provided by a crew member's body weight (1/6 g), or by body weight with spacesuit weight included (~1/3 g), would be enough to mitigate losses of bone and muscle. A manuscript has been revised and submitted to the journal *Medicine and Science in Sports and Exercise* and is still in review. These results confirm our original findings that 1/3 g is partially protective of cortical but not cancellous bone and that, for most bone outcomes, 1/6 and 1/3 BW loading do not prevent decrements in bone integrity observed with full hindlimb unloading (simulating, e.g., low-Earth orbit).

Continuing data analyses on experiments supporting Specific Aim 2 [Determine impact of low-dose, high LET radiation exposure (modeling that expected on the Lunar surface) on musculoskeletal outcomes in modeled Lunar gravity conditions] allowed for more refinement of conclusions reached during year 3. In support of our original hypothesis, radiation exposure exacerbates the loss of cancellous bone (%BV/TV) seen with partial weightbearing; it took only 0.5 Gy of 28Si exposure to produce the same 14% decline in %BV/TV as observed with 1 Gy of reference x-ray radiation. The primary effect on cancellous bone microarchitecture was a decrease in trabecular number but not trabecular thickness, suggesting more of an effect on osteoclast resorptive activity than on osteoblast formation activity, consistent with published literature. One of our most intriguing results was that fractionating the 0.5 Gy 28Si dose into 3 doses spread over the period of PWB produced the same net bone loss as did one acute dose delivered on the first day of PWB. By contrast, fractionating our 1 Gy x-ray exposure into 3 exposures DID effectively mitigate loss of bone.

The major task accomplished in Year 4 of this project was to complete experiments supporting our final specific aim: would low dose, high LET radiation impair the ability of bone and muscle to respond to exercise during recovery from a period of simulated Lunar gravity conditions? Marshaling all available budgetary means, we returned to NSRL at Brookhaven to test impact of simulated GCR on the exercise response in bone and muscle, rather than relying on reference (x-ray) radiation. During NSRL's Fall 2011 run, we successfully exposed ~65 mice to acute dose (0.5 Gy) of 56-Fe, before they were shipped to Texas A&M, where the animal protocols were conducted, finishing in April 2012. We have generated some exciting and novel data on vertebral bone responses to PWB and recovery there from: the 0.5 Gy 56Fe exposure appears to significantly impair the ability of spinal bone to regain cancellous bone mass lost during the preceding period of PWB. In fact, further losses in trabecular thickness are observed during the recovery period (with and without exercise), implying a sustained suppression of osteoblast activity from the radiation exposure imposed 6 weeks earlier. Similar findings held for cancellous bone in the distal femur, but the effects are less dramatic than in vertebral bone. Preliminary assessment of bone formation rate (BFR) on the periosteal surface of the tibial shaft indicates a significant reduction in this marker of osteoblast activity in this separate bone compartment. On-going histomorphometric analyses of BFR in the distal femur will help verify if high LET radiation also suppresses osteoblast function some 6 weeks later in cancellous bone.

We have also produced some novel data regarding skeletal muscle outcomes from combined partial weightbearing and simulated galactic cosmic radiation exposure. Simulated Lunar gravity resulted in significant decreases in muscle mass and rates of muscle protein synthesis. However, contrary to the working hypothesis, both ion species used (0.5 Gy 28Si, 300 MeV or 0.5 Gy 56Fe, 1 GeV), contributed to an increase in muscle wet mass. In viable muscle, alterations of muscle mass are associated with alterations of protein content that are proportional with water content. Thus, in healthy muscle, changes in muscle mass do not lead to changes in protein concentration within the tissue. Our analyses reveal that protein concentration was constant among groups in the 28Si groups, but not 56Fe groups. Furthermore, it appears that alterations in fractional synthesis rates (assessed using novel deuterium-oxide methodologies) were consistent with changes in protein concentrations, where lower FSRs were documented in tissues with lower protein concentrations. In summary, our results verify that the increases in gastrocnemius wet mass exposed to 0.5 Gy of 300 MeV 28Si are reflective of muscle gains, with or without the presence of partial loading. Gains due to 50cGy exposure of 1 GeV 56Fe appear to indicate an accumulation of extraneous, non-protein substances. These experiments were designed to answer IRP Risk Degen 7 ["Are there significant synergistic effects from other spaceflight factors (microgravity, stress, altered circadian rhythms, changes in immune responses, etc.) that modify the degenerative risk from space radiation?"] in addition to IRP Risk B11 ["What are the effects of radiation on bone?"] Understanding the interaction of reduced weightbearing and radiation exposure is an important goal in support of human exploration of space. Although not designed to thoroughly explain mechanisms for observed effects on bone and skeletal muscle, we are generating supporting analyses to provide some insight to direct future investigations.

## Rationale for HRP Directed Research:

Defining the impact of partial weightbearing (as opposed to complete non-weightbearing) has important implications for rehabilitative strategies applied to stroke or spinal cord-injured patients. Our results indicate that weightbearing at 1/6 or 1/3 of normal body weight does NOT mitigate the dramatic loss of mass and strength in both muscle and bone seen with zero load bearing (mimicking conditions of low-Earth orbit, e.g.). This implies that additional strategies beyond partial weightbearing that can be achieved with harness systems or walkers (such as active exercise of the affected limbs) is necessary to help minimize or reverse disuse-induced loss of muscle strength and bone integrity. Another population that stands to benefit from these data is composed of veterans returning home with traumatic brain injury, a major concern of the military these last 7 years.

## Research Impact/Earth Benefits:

Our experiments focusing on effects of low-dose radiation on musculoskeletal structure and function provide unique and novel data about the potential degenerative effects to be expected by those humans living in areas with high natural background radiation (e.g., Ramsar, Iran); by individuals who accumulate high occupational exposures to ionizing radiation (e.g., commercial airplane crews); and by patients accumulating multiple medical irradiation exposures over time. A growing literature is documenting surprising and deleterious effects on bone with low-level radiation (as opposed to the high doses used in radiotherapy for cancer patients) and our results are consistent with those findings, especially in bone sites rich in cancellous bone, such as the femoral neck (site of hip fractures) and in vertebral bone. Very little is known at the present time about the impact on these low doses on maintenance of normal muscle protein synthesis and muscle mass. Our early results suggest a surprising (but small) gain in muscle mass with very low dose, high LET radiation exposure, even during a period of partial weightbearing. However, protein synthesis appears to be impaired, so these gains in mass may not reflect gains in functional tissue (perhaps connective tissue).

<p><b>Task Progress:</b></p>	<p>Specific Aim 1: We reworked a previously rejected manuscript extensively, adding new data, and submitted it in Dec 2012 to the journal Medicine and Science in Sports and Exercise.</p> <p>Specific Aim 2 (impact of low-dose, high energy radiation simulating galactic cosmic radiation): All experiments were completed earlier; during Year 4 of this project we focused on finalizing histomorphometry analyses, muscle protein synthesis determinations and started on manuscript preparation. Experiment 2 (pilot experiment testing various doses of x-ray radiation in weightbearing mice, with primary cell culture studies) manuscript is in preparation for submission to the journal Radiation Research; progress has been slowed by the departure of the post-doctoral fellow (F. Lima) in charge, who has committed to a February, 2013 deadline. A second manuscript targeted to Radiation Research is being submitted in March 2013 detailing the impact of x-ray and high LET (28-Si) radiation exposures on cortical bone (B.R. Macias, first author); some of these data were also presented at the International Congress of Radiation Research (Warsaw, Poland; August, 2011) and at the American Society for Bone and Mineral Research, Annual Meeting (San Diego, CA; September, 2011). At least one other bone-oriented manuscript will be submitted as soon as we finalize the more labor-intensive histomorphometry analyses on cancellous bone from these experiments. Muscle protein synthesis and related cell signaling data (by Western blot) collection is now complete; histological assays for BrdU incorporation and fiber-type specific cross-sectional areas are in progress and should provide compelling data for several more manuscripts.</p> <p>Specific Aim 3 (impact of simulated GCR on bone/muscle response to exercise during recovery from a period of partial weightbearing(PWB): We completed an extensive pilot experiment in summer of 2011 comparing the efficacy of two exercise paradigms in mitigating bone loss during a PWB period: treadmill running (endurance training) vs. tower climbing (more resistance based). (A manuscript of these data will be ready for submission to Acta Astronautica in late February, 2013; R. Boudreaux, first author.) Marshaling all available budgetary means, we returned to NSRL at Brookhaven to test impact of simulated GCR on the exercise response in bone and muscle, rather than relying on reference (x-ray) radiation. During NSRL's Fall 2011 run, we successfully exposed ~65 mice to acute dose (0.5 Gy) of 56-Fe, before they were shipped to Texas A&amp;M, where the animal protocols were conducted, finishing in April 2012. All micro-CT analyses were finished by December 2012, as well as some mechanical testing results. On-going are histomorphometry analyses and skeletal muscle histology. We anticipate 2-3 more manuscripts will result from these data within the next 6 months.</p>
<p><b>Bibliography Type:</b></p>	<p>Description: (Last Updated: 05/28/2021)</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Camp KA, Cunningham DA, Yuen E, Macias B, Solomon S, Hogan HA, Bloomfield SA. "Impact of omega-3 polyunsaturated fatty acids on bone during chronic simulated resistance training." 33rd Annual Meeting of the American Society for Bone and Mineral Research, San Diego, California, September 16-20, 2011. J Bone Miner Res. 2011;26(Suppl 1). , Sep-2011</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Cunningham DA, Camp KA, Yuen E, Macias B, Solomon S, Hogan HA, Bloomfield SA. "Ibuprofen administered pre- or post-simulated resistance exercise training does not diminish gains in bone formation or bone mass." 33rd Annual Meeting of the American Society for Bone and Mineral Research, San Diego, California, September 16-20, 2011. J Bone Miner Res. 2011;26(Suppl 1). , Sep-2011</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Yuen E, Morgan J, Zwart SR, Gonzales E, Camp K, Macias BR, Smith SM, Bloomfield SA. "High dietary iron and 137Cs radiation exposure induce oxidative stress and reduce bone mass." Experimental Biology 2012, San Diego, CA, April 21-25, 2012. FASEB Journal. 2012 Apr;26(Meeting Abstract Supplement):641.28. , Apr-2012</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Macias BR, Yuen E, Camp K, Boudreaux R, Metzger C, Morgan S, Shirazi-Fard Y, Hogan HA, Bloomfield S. "Inhibition of Glycogen Synthase Kinase-3<math>\beta</math> Combined with Simulated Resistance Exercise during Hindlimb Unloading Prevents Femoral Neck and Mid-Shaft Tibia Cortical Bone Loss." 4th Joint Meeting of the European Calcified Tissue Society and International Bone and Mineral Society; Stockholm, Sweden, May 19-23, 2012. Bone. 2012 May;50(Suppl 1):S124. <a href="http://dx.doi.org/10.1016/j.bone.2012.02.385">http://dx.doi.org/10.1016/j.bone.2012.02.385</a> , May-2012</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Macias RM, Lima F, Shirazi-Fard Y, Cunningham DA, Yuen E, Camp K, Wiggs MP, Fluckey JD, Greene ES, Allen MR, Braby LA, Hogan HA, Bloomfield SA. "Partial weightbearing for 21-days and low dose high energy radiation results in cancellous and cortical bone loss." 33rd Annual Meeting of the American Society for Bone and Mineral Research, San Diego, California, September 16-20, 2011. J Bone Miner Res. 2011;26(Suppl 1). , Sep-2011</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Shimkus KL, Wiggs M, Macias BR, Lima F, Boudreaux RD, Shirazi-Fard Y, Greene E, Braby L, Hogan HA, Bloomfield SA, Fluckey J. "Space Radiation Environment Increases Muscle Mass in Simulated Lunar Gravity." 2012 APS Intersociety Meeting: Integrative Biology of Exercise, Westminster, CO, October 10-13, 2012. 2012 APS Intersociety Meeting: Integrative Biology of Exercise, Westminster, CO, October 10-13, 2012. Program and Abstracts, Abstract 23.1, p. 41. , Oct-2012</p>
<p><b>Abstracts for Journals and Proceedings</b></p>	<p>Boudreaux R, Metzger C, Cecchini T, Camp K, Yuen E, Macias B, Shirazi-Fard Y, Hogan H, Bloomfield S. "Treadmill Running and Tower Climbing Resistance Exercise Mitigate Disuse Bone Loss in Mice Equally Well." Texas Chapter of the American College of Sports Medicine 2012 meeting, Austin, TX, March 1-2, 2012. International Journal of Exercise Science: Conference Abstract Submissions: 2012;2(4):Article 3. Available at: <a href="http://digitalcommons.wku.edu/ijesab/vol2/iss4/3">http://digitalcommons.wku.edu/ijesab/vol2/iss4/3</a> , Mar-2012</p>
<p><b>Articles in Peer-reviewed Journals</b></p>	<p>Macias BR, Swift JM, Nilsson MI, Hogan HA, Bouse SD, Bloomfield SA. "Simulated resistance training, but not alendronate, increases cortical bone formation and suppresses sclerostin during disuse." J Appl Physiol. 2012 Mar;112(5):918-25. Epub 2011 Dec 15. <a href="http://dx.doi.org/10.1152/jappphysiol.00978.2011">http://dx.doi.org/10.1152/jappphysiol.00978.2011</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/22174402/">PMID: 22174402</a> , Mar-2012</p>
<p><b>Articles in Peer-reviewed Journals</b></p>	<p>Swift JM, Hogan HA, Bloomfield SA. "<math>\beta</math>-1 Adrenergic agonist mitigates unloading-induced bone loss by maintaining formation." Med Sci Sports Exerc. 2013 Sep;45(9):1665-73. <a href="https://doi.org/10.1249/MSS.0b013e31828d39bc">https://doi.org/10.1249/MSS.0b013e31828d39bc</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/23470310/">PMID: 23470310</a> , Sep-2013</p>

Articles in Peer-reviewed Journals	Boudreaux RD, Metzger CE, Macias BR, Shirazi-Fard Y, Hogan HA, Bloomfield SA. "Bone loss during partial weight bearing (1/6th gravity) is mitigated by resistance and aerobic exercise in mice." Acta Astronaut. 2014 Jun-Jul;99:71-7. <a href="http://dx.doi.org/10.1016/j.actaastro.2014.02.015">http://dx.doi.org/10.1016/j.actaastro.2014.02.015</a> , Jun-2014
Articles in Peer-reviewed Journals	Boudreaux RD, Swift JM, Gasier HG, Wiggs MP, Hogan HA, Fluckey JD, Bloomfield SA. "Increased resistance during jump exercise does not enhance cortical bone formation." Med Sci Sports Exerc. 2014;46(5):982-9. <a href="http://dx.doi.org/10.1249/MSS.0000000000000195">http://dx.doi.org/10.1249/MSS.0000000000000195</a> ; PubMed <a href="#">PMID: 24743108</a> ; PubMed Central <a href="#">PMCID: PMC3992436</a> , Jan-2014
Articles in Peer-reviewed Journals	Swift SN, Swift JM, Bloomfield SA. "Mechanical loading increases detection of estrogen receptor-alpha in osteocytes and osteoblasts despite chronic energy restriction." J Appl Physiol (1985). 2014 Dec 1;117(11):1349-55. Epub 2014 Sep 11. <a href="http://dx.doi.org/10.1152/japplphysiol.00588.2013">http://dx.doi.org/10.1152/japplphysiol.00588.2013</a> ; PubMed <a href="#">PMID: 25213639</a> , Dec-2014
Articles in Peer-reviewed Journals	Macias BR, Lima F, Swift JM, Shirazi-Fard Y, Greene ES, Allen MR, Fluckey J, Hogan HA, Braby L, Wang S, Bloomfield SA. "Simulating the lunar environment: Partial weightbearing and high-LET radiation-induce bone loss and increase sclerostin-positive osteocytes." Radiat Res. 2016 Sep;186(3):254-63. <a href="http://dx.doi.org/10.1667/RR13579.1">http://dx.doi.org/10.1667/RR13579.1</a> ; PubMed <a href="#">PMID: 27538114</a> , Sep-2016
Articles in Peer-reviewed Journals	Lee TV, Lee CW, Chen VCW, Bui S, Fluckey JD, Riechman SE. "The effects of hindlimb unloading versus dietary cholesterol and resistance training on rat skeletal muscle responses." Lipids Health Dis. 2019 Jan 5;18(1):3. <a href="https://doi.org/10.1186/s12944-018-0944-9">https://doi.org/10.1186/s12944-018-0944-9</a> ; PubMed <a href="#">PMID: 30611265</a> ; PubMed Central <a href="#">PMCID: PMC6320614</a> , Jan-2019
Articles in Peer-reviewed Journals	Lima F, Swift JM, Greene ES, Allen MR, Cunningham DA, Braby LA, Bloomfield SA. "Exposure to low-dose X-ray radiation alters bone progenitor cells and bone microarchitecture." Radiat Res. 2017 Oct;188(4):433-42. Epub 2017 Aug 3. <a href="https://doi.org/10.1667/RR14414.1">https://doi.org/10.1667/RR14414.1</a> ; PubMed <a href="#">PMID: 28771086</a> , Oct-2017
Awards	Macias B. "NSBRI Post-Doctoral Fellowship, October 2012." Oct-2012
Awards	Macias B. "Texas A&M Dept of Health & Kinesiology Distinguished Honor Graduate Student, December 2012." Dec-2012
Awards	Elmer K. "Texas A&M College of Education Undergraduate Research Award, September 2012." Sep-2012
Awards	Boudreaux R. "NSBRI Pre-Doctoral Space Life Science Fellowship, January 2012." Jan-2012
Awards	Boudreaux R. "Texas Space Grant Fellowship, June 2012." Jun-2012
Awards	Wang S. "Editor-in-Chief, Journal of Nonparametric Statistics, December 2011." Dec-2011
Books/Book Chapters	Bloomfield SA, Metzger CE. "Novel findings in bone biology: impact on bone health for women." in "Integrative Physiology of Women's Health." Ed. E. Spangenberg. New York : Springer, 2013. p. 17-33. <a href="https://doi.org/10.1007/978-1-4614-8630-5_2">https://doi.org/10.1007/978-1-4614-8630-5_2</a> , Sep-2013