Fiscal Year:	FY 2012	**Task Last Updated:**	FY 04/04/2013
PI Name:	Bloomfield, Susan A. Ph.D.		
Project Title:	Maintaining Musculoskeletal Health in the Lunar Environment		
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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City:	College Station	**State:**	TX
Zip Code:	77843-4375	**Congressional District:**	17
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2007 Crew Health NNJ07ZSA002N
Start Date:	06/01/2008	**End Date:**	09/30/2012
No. of Post Docs:	0	**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:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date change to 9/30/2012 (from 5/31/2012) per NSBRI (Ed., 1/24/2012)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Braby, Leslie (Texas Engineering Experiment Station) Hogan, Harry (Texas A&M University) Fluckey, James (Texas A&M University) Wang, Suojin (Texas A&M University)		
Grant/Contract No.:	NCC 9-58-MA01602		
Performance Goal No.:			
Performance Goal Text:			

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 Gy28Si, 300 MeV or 0.5 Gy 56Fe, 1GeV), 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:	
Research Impact/Earth Benefits:	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. 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).

Task Progress:	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. 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 BrdUincorporation and fiber-type specific cross-sectional areas are in progress and should provide compelling data for several more manuscripts. 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&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.
Bibliography Type:	Description: (Last Updated: 05/28/2021)
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