Fiscal Year:	FY 2014	**Task Last Updated:**	FY 03/26/2015
PI Name:	Hogan, Harry Ph.D.		
Project Title:	Can Benefits from a Single Administration of Bisphosphonates Extend to a Second Later Exposure to Microgravity?		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
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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Zip Code:	77843-3123	**Congressional District:**	17
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2012 Crew Health NNJ12ZSA002N
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No. of Post Docs:	0	**No. of PhD Degrees:**	1
No. of PhD Candidates:	2	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NASA ARC
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Flight Program:			
Flight Assignment:	NOTE: Start date changed to 9/30/2013 per discussions with A. Chu/ARC (Ed., 7/9/14)		
Key Personnel Changes/Previous PI:	none		
COI Name (Institution):	Bloomfield, Susan Ph.D. (Texas A&M University)		
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	Two recent trends in International Space Station (ISS) crew member patterns is that more are making repeat flights into space and some have begun using osteoporosis drugs as a countermeasure to the negative effects of microgravity on the skeletal system. This pilot project aims to provide new data that can help better understand the effects of multiple missions on those crew members who have taken such osteoporosis drugs as part of a previous mission, or who might be considering this in the future. Initial results have shown impressive benefits. Selected crew members have taken alendronate, which is a popular osteoporosis drug from the class known as bisphosphonates, just before and during their ISS missions and have reported much milder effects on bone density. Based on the mechanisms of action for this class of drugs, it is plausible, and perhaps even likely, that the benefits gained from taking alendronate for one mission could actually extend into a second mission without further treatment at all. The goal of the proposed research is to address this		

Task Description:	question directly by using the well-established, ground-based analog: the adult hindlimb unloaded (HU) rat model. We have conducted an extensive set of experiments for NASA in recent years using this model to examine multiple exposures to microgravity but none of these included the osteoporosis drugs. In the current project, we will determine the effects of a single administration of bisphosphonates on adult male rats exposed to two successive HU exposures, with a period of recovery between the two. The focus will be to compare the effects of the second HU on the group of animals that has been administered alendronate concurrently with the first HU exposure with those that have not. We will quantify bone mineral content, bone mineral density, and various measures of cross-sectional geometry and shape using X-ray based scanning conducted every 28 days on anesthetized living animals. We will also measure bone strength and histological parameters on tissue specimens harvested at the end of the study. Completion of the studies outlined in this proposal will provide critical new findings quantifying the possible persistent beneficial effects of a single bisphosphonate treatment on a second later exposure to microgravity. These findings are strongly relevant to care and planning for current ISS crewmembers. The key deliverable in this regard will be the knowledge gained and the promising prospects for translating this directly to assessment of current and future ISS crew member missions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Results from this project will provide fundamental understanding of the way bone responds to mechanical unloading and how it recovers when mechanical loads are restored. Insights gained should be applicable to the clinically relevant case of aging adults with reduced activity levels, in addition to the effects of long term exposure to microgravity for crew members. Further, many of the same basic mechanisms overlap considerably with the broader health problem of osteoporosis and increased fracture risk in aging humans. Completion of the studies outlined in this research proposal will provide new insights into the basic nature of the effects of pharmaceutical (bisphosphonates) countermeasures. Questions to be addressed will directly supplement recent, and continuing, research on crewmembers taking alendronate. In addition, newer bisphosphonates such as zoledronic acid have generally higher potency than alendronate, so there is interest in how the two drugs would compare. These comparisons will benefit understanding of the effects of drug withdrawal, or holidays, for the more general clinical population on Earth.
Task Progress:	Bone response to multiple exposures of microgravity remains a concern for astronauts. More astronauts are making repeat flights, and some have taken the bisphosphonate alendronate (ALN) to prevent bone loss during flight. Given the long-lasting effects of these drugs, it is possible that protection may persist for subsequent flights. In addition, newer bisphosphonates such as zoledronic acid (ZOL) have generally higher potency than alendronate, so there is interest in how the two drugs would compare in this kind of scenario. Findings generated should have clinical relevance more broadly and also help understand and mitigate risks associated with human exploration of space. The primary risks addressed by this research are: (a) Risk of Bone Fracture, and (b) Risk of Early Onset Osteoporosis Due To Spaceflight. The adult hindlimb unloaded (HU) rat model was used to simulate two successive missions using a modification of the Morey-Holton method of tail traction. In this model, the animal is suspended by the tail through the use of a custom-made harness attached to the tail to remove weight-bearing loads from the hindlimbs of the animal. The height of the animal's hindquarters was adjusted to prevent any contact of the hindlimbs with the cage floor, resulting in approximately a 30° head-down tilt. The forelimbs of the animal maintain contact with the cage floor allowing the rat full access to the entire cage. Adult Sprague-Dawley male rats 6 months of age were block assigned to aging control (AC) and HU groups by body weight. HU animals were exposed to 28 days of HU, followed by 56 days of recovery, and then a second 28-day HU exposure. Subsets of HU animals were administered ALN (ALN+HU), ZOL (ZOL+HU), or nothing (HUC) for the initial 28d of HU only. ALN (2.4 µg/kg) was injected 3x/week for 5 weeks, starting the week before the first HU. ZOL (60 µg/kg) was injected in a single dose prior to the first HU. In vivo peripheral quantitative computed tomography (pQCT) scans were taken of the proximal tibia metaphysis (PTM) at baseline (BL) and every 28 days. This research was supported through the Omnibus mechanism, with the entire duration of the project therefore limited to only 1 year. Accordingly, more comprehensive and destructive ex vivo tests and analyses were conducted only at the final time point at the end of the study, following the 2nd HU period (day 112). For in vivo pQCT results, ALN prevented losses for the first HU, as both total bone mineral content (BMC) and volumetric bone mineral density (vBMD) for HU+A were not different from baseline (BL) or AC at day 28. In contrast, ZOL induced absolute gains in both total BMC and vBMD, with HU+Z significantly higher after the first HU compared to BL, AC, and HUC. The efficacy of ZOL continued throughout the 56d recovery period, with both total BMC and vBMD significantly higher for HU+Z compared to BL, AC, HUC, and HU+A. For the second HU, total vBMD was unchanged for HU+Z and remained significantly higher than BL (+14.2%), AC (+13.7%), HUC (+16.2%), and HU+A (+10.7%). For HU+A, total vBMD was not different from AC at the start and end of the second HU. Additional tests and analyses were conducted on specimens harvested from animals at the end of the study (day 112). For these ex vivo results, bone volume fraction (BV/TV) from microCT was significantly higher for HU+Z compared to BL, AC, HUC, and HU+A; however, BV/TV values were not different for HU+A compared to BL, AC, or HUC. Trabecular thickness (Tb.Th) was higher for HU+Z than HUC and HU+A, but not different from BL or AC. For HU+A, Tb.Th was not different from BL, AC, or HUC. These microarchitectural parameters of the trabecular compartment demonstrate the superior potency of ZOL, whereas ALN was not beneficial for these measures. For ex vivo mechanical testing, the femoral neck (FN) maximum fracture load was significantly higher for HU+Z compared to every other group, with no other statistical differences. Maximum fracture loads from 3-point bending of both the tibia and femur were significantly higher for HUC, HU+Z, and HU+A compared to BC. Results from this unique study design support the hypothesis that beneficial effects of both ALN and ZOL do extend to the second HU exposure when treatments were given for the first HU only. ALN was generally protective for both HU bouts as reflected by in vivo pQCT measures. ZOL was broadly more robust in enhancing a wide range of parameters for both in vivo and ex vivo measures, including cortico-cancellous region densitometric properties, trabecular microarchitecture, and mechanical properties. ZOL benefits appear to be mainly due to bone accrual during the first HU that continued for the 56-day recovery period. These findings suggest that crew members taking a bisphosphonate for one ISS mission may experience benefits for subsequent missions without repeating treatments. More detailed comparisons of alendronate (ALN) and zolendronic acid (ZOL) are continuing, as additional mechanical testing and histological analyses are underway and will not be completed for several more months. Newest results will be further disseminated through conferences (ASBMR and ASGSR), as well as submitted for

	journal publication.
Bibliography Type:	Description: (Last Updated: 01/11/2021)
Abstracts for Journals and Proceedings	Lenfest SE, Brezicha JE, Boudreaux RD, Schaefer CM, Bloomfield SA, Allen MR, Hogan, HA. "Bisphosphonate Treatment During an Initial Unloading Period Also Protects Against Bone Loss for a Second Unloading." 36th Annual Meeting of the American Society for Bone and Mineral Research, Houston, Texas, September 12-15, 2014. 36th Annual Meeting of the American Society for Bone and Mineral Research, Houston, Texas, September 12-15, 2014. Poster Presentation SU0036. , Sep-2014
Abstracts for Journals and Proceedings	Lenfest SE, Brezicha JE, Boudreaux RD, Schaefer CM, Bloomfield SA, Allen MR, Hogan HA. "Benefits of Bisphosphonate Treatment During an Initial Unloading Period Extends to a Second Unloading Period." Poster Presentation (IP.37). 30th Annual Meeting of the American Society for Gravitational and Space Research, Pasadena, CA, October 22-26, 2014. 30th Annual Meeting of the American Society for Gravitational and Space Research, Pasadena, CA, October 22-26, 2014. , Oct-2014
Abstracts for Journals and Proceedings	Lenfest SE, Brezicha JE, Narayanan A, Reyna W, Bloomfield SA, Allen MR, Hogan HA. "Comparison of Protective Effects of Alendronate and Zoledronic Acid for Two Successive Unloading Exposures." Poster Presentation. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. Abstract #0044. , Jan-2015