Fiscal Year:	FY 2022	**Task Last Updated:**	FY 07/28/2021
PI Name:	Rutkove, Seward M.D.		
Project Title:	Approaching Gravity As a Continuum: Musculoskeletal Effects of Fractional Reloading		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	(1) Animal Biology: Vertebrate		
Space Biology Cross-Element Discipline:	(1) Musculoskeletal Biology		
Space Biology Special Category:	(1) Translational (Countermeasure) Potential		
PI Email:	srutkove@bidmc.harvard.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	617-667-8130
Organization Name:	Beth Israel Deaconess Medical Center, Inc./Harvard Medical School		
PI Address 1:	330 Brookline Ave TCC-810		
PI Address 2:			
PI Web Page:			
City:	Boston	**State:**	MA
Zip Code:	02215-5400	**Congressional District:**	7
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2018 Space Biology (ROSBio) NNH18ZTT001N-FG. App B: Flight and Ground Space Biology Research
Start Date:	10/01/2019	**End Date:**	09/30/2022
No. of Post Docs:	2	**No. of PhD Degrees:**	2
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NASA ARC
Contact Monitor:	Griko, Yuri	**Contact Phone:**	650-604-0519
Contact Email:	Yuri.V.Griko@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	None		
COI Name (Institution):	Bouxsein, Mary Ph.D. (Beth Israel Deaconess Medical Center, Inc./Harvard Medical School)		
Grant/Contract No.:	80NSSC19K1598		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The effect of full mechanical unloading has been extensively studied in both rodents and humans using ground-based models. Recently, rodent partial weight bearing (PWB) models have revealed that partial gravity provides dose-dependent rescue of the musculoskeletal system as compared to full unloading. Separate work has also shown that after unloading, an abrupt mechanical reloading to 1g causes additional musculoskeletal injury. Here, we propose to employ both PWB and hindlimb unloading models sequentially to investigate gravity as a continuum and its impact on musculoskeletal adaptation to reloading. This work will have critical practical and scientific outcomes, and will provide for the first time, insights into the musculoskeletal responses to adult to fractional gravity after a period of microgravity (as would occur when traveling to Mars). It will also provide information on the mitigating effects of partial gravity after extended unloading. Our Specific Aims are: 1) To determine the physiological adaptations of the musculoskeletal system in males to the fractional gravity of either the Moon or Mars after experiencing microgravity in transit, 2) To determine the physiological adaptations of the musculoskeletal system in females to the fractional gravity of either the Moon or Mars after experiencing microgravity in transit, and 3) To investigate the potential musculoskeletal benefits of artificial gravity in-flight before returning to Earth. Specifically, we plan to investigate the resulting musculoskeletal alterations in transitioning from 2 weeks of 0g to 0.2, 0.4, and 0.7g, hypothesizing that there is a dose-dependence to the reloading, including recovery and associated injury. We will also assess the potential benefit of using these three levels of PWB as intermediate steps on the way to transitioning back to 1g. Thorough post mortem analyses, we will be able to identify the different processes that might be involved in reloading injury and its mitigation. Stress levels and metabolic/hormonal alterations will also be evaluated. Ultimately, we hope to provide the space biology community a deeper understanding of the musculoskeletal impact of fractional gravity in relation to both microgravity and Earth gravity.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research will have important implications for the improved understanding of the effects of prolonged disuse on bone and muscle due to bedrest or injury and the effects of rehabilitation. Specifically, lessons learned from this work may help us better understand the negative impact of the re-establishing normal activity after the development of disuse atrophy and the potential for applying graded rehabilitation approaches so as to ensure effective recovery.
Task Progress:	Following the COVID-19 pandemic and laboratory shutdown, in vivo experiments have been delayed in 2020. During the first semester (July 2020-December 2020), we worked towards completion of the Aim 1, by assessing how males adjust to partial reloading at 20, 40, and 100% of weight-bearing following an extensive time spent in a microgravity analogue, and thus disused. As our goal was to assess the existence of a “reloading injury” following disuse, as would be the case when astronauts would land on the Moon, Mars, or Earth following a trip in space, animals were re-ambulated for either 4 or 24 hours and monitored. We did not encounter methodological problems during this experiment and successfully completed all groups by the end of 2020. Separately, we assessed the impact of disuse on female rats compared to normally-loaded controls, and analyzed all results both in vivo and ex vivo. Therefore, we were able to compare if males and females respond similarly to disuse-induced muscular deconditioning, and submitted a manuscript reflecting our findings in 2021. The manuscript is currently under revision. In the second semester (January 2021-June 2021), we focused on “reloading injury” following disuse in female animals (Aim 2). We used a paradigm strictly identical to what has been done previously with male rats, and successfully completed the 4 and 24 hours groups for females. Ex vivo analyses have been completed and a manuscript recapitulating the neuromuscular changes in both sexes is currently in preparation, and should be submitted for publication shortly. Moreover, we explored the potential relationship between estrous cycle maintenance and musculoskeletal functions using both animals from our current project and previous results. The findings have been summarized in a manuscript that has been submitted for publication in 2021. Overall, our work this year has aimed to highlight how sex influences animals adaptation to musculoskeletal disuse, and if partial reloading significantly impacts musculoskeletal health.
Bibliography Type:	Description: (Last Updated: 03/05/2024)
Abstracts for Journals and Proceedings	Rosa-Caldwell ME, Mortreux M, Sung DM, Schreurs AS, Bouxsein ML, Rutkove SB. "Low testosterone status differentially affects musculoskeletal outcomes after exposure to micro- or partial gravity." 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. Abstracts. 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. , Nov-2020
Abstracts for Journals and Proceedings	Mortreux M, Rosa-Caldwell ME, Sung DM, Stiehl ID, Rutkove SB. "Early adaptation to increased mechanical loading after disuse: muscular response in male and female rats." 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. Abstracts. 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. , Nov-2020
Articles in Peer-reviewed Journals	Rosa-Caldwell ME, Mortreux M, Kaiser UB, Sung DM, Bouxsein ML, Dunlap KR, Greene NP, Rutkove SB. "The oestrous cycle and skeletal muscle atrophy: Investigations in rodent models of muscle loss." Exp Physiol. 2021 Sep 26. https://doi.org/10.1113/EP089962 ; PMID: 34569104; PMCID: PMC8639792 , Sep-2021
Articles in Peer-reviewed Journals	Mortreux M, Rosa-Caldwell ME, Stiehl ID, Sung DM, Thomas NT, Fry CS, Rutkove SB. "Hindlimb suspension in Wistar rats: Sex-based differences in muscle response." Physiol Rep. 2021 Oct;9(19):e15042. https://doi.org/10.14814/phy2.15042 ; PMID: 34612585; PMCID: PMC8493566 , Oct-2021

Articles in Peer-reviewed Journals	Mortreux M, Rosa-Caldwell ME. "Approaching gravity as a continuum using the rat partial weight-bearing model. " Life. 2020 Oct 8;10(10):235. Review. https://doi.org/10.3390/life10100235 ; PMID: 33049988; PMCID: PMC7599661 , Oct-2020
Articles in Peer-reviewed Journals	Malkani S, Chin CR, Cekanaviciute E, Mortreux M, Okinula H, Tarbier M, Schreurs AS, Shirazi-Fard Y, Tahimic CGT, Rodriguez DN, Sexton BS, Butler D, Verma A, Bezdan D, Durmaz C, MacKay M, Melnick A, Meydan C, Li S, Garrett-Bakelman F, Fromm B, Afshinnekoo E, Langhorst BW, Dimalanta ET, Cheng-Campbell M, Blaber E, Schisler JC, Vanderburg C, Friedländer MR, McDonald JT, Costes SV, Rutkove S, Grabham P, Mason CE, Beheshti A. "Circulating miRNA spaceflight signature reveals targets for countermeasure development." Cell Rep. 2020 Dec 8;33(10):108448. https://doi.org/10.1016/j.celrep.2020.108448 ; PMID: 33242410 , Dec-2020
Articles in Peer-reviewed Journals	Willey JS, Britten RA, Blaber E, Tahimic CGT, Chancellor J, Mortreux M, Sanford LD, Kubik AJ, Delp MD, Mao XW. "The individual and combined effects of spaceflight radiation and microgravity on biologic systems and functional outcomes." J Environ Sci Health C Toxicol Carcinog. 2021 Apr 27;39(2):129-79. https://doi.org/10.1080/26896583.2021.1885283 ; PMID: 33902391; PMCID: PMC8274610 , Apr-2021