Fiscal Year:	FY 2024	**Task Last Updated:**	FY 07/23/2023
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		
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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:**	1
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
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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)		
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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:	We completed all proposed experiments in males and female rats, aiming at understanding the acute and mid-term adaptation to mechanical reloading following disuse (mimicking microgravity). Moreover, we assessed if partial gravity could be a useful countermeasure when implemented during a mission (by simulating different artificial gravity protocol on the Gateway station, for example). All in vivo and ex vivo analyses have been completed – including muscle function, force production, physiological measurements, muscle histomorphometry, and gene expression using reverse transcription-quantitative polymerase chain reaction (RTqPCR). Organs have been collected and stored for further analysis and for future shipping to the NASA Ames Life Science Data Archive (ALSDA) storage facility. Bone analysis has been performed using peripheral quantitative computed tomography (pQCT) and micro computed tomography (microCT), and serum levels of several bone biomarkers have been performed. Overall, our work demonstrates that males and females react differently to mechanical reloading following disuse, and that bone deconditioning seems to be dramatically impacted by biological sex both during disuse and recovery. For example, we exposed male and female animals to 14 days of hindlimb unloading to induce musculoskeletal deconditioning, before reloading them at 1g for 7d. During the disuse period, females showed a 7% decline in bone mineral density, which was not significantly different than their baseline values. On the other hand, males bone density declined by 20% during the same period, highlighting the greater susceptibility to disuse-induced bone loss in males. While we assumed that 7d of mechanical reloading would lead to bone growth, we did not observe it. Indeed, in males, bone loss continued during the recovery period, at almost an identical rate (approx. -10%/wk).
Bibliography Type:	Description: (Last Updated: 03/05/2024)
Abstracts for Journals and Proceedings	Issertine M, Rosa-Caldwell ME, Sung DM, Bouxsein ML, Rutkove SB, Mortreux M. "Adaptation to full weight-bearing following disuse: The impact of biological sex on musculoskeletal health. " 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. Abstracts. 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. , Feb-2023
Abstracts for Journals and Proceedings	Mortreux M, Rosa-Caldwell ME, Sung DM, Issertine M, Rutkove SB. "Assessing the benefits of artificial gravity on the Gateway: An analog study in males." 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. Abstracts. 2023 NASA Human Research Program Investigators' Workshop, "To the Moon: The Next Golden Age of Human Spaceflight", Galveston, TX, February 7-9, 2023. , Feb-2023
Abstracts for Journals and Proceedings	Issertine M, Rosa-Caldwell ME, Sung DM, Bouxsein ML, Rutkove SB, Mortreux M. "Adaptation to full weight-bearing following disuse: The impact of biological sex on musculoskeletal health." 38th Annual Meeting of the American Society for Gravitational and Space Research, Houston, TX, November 9-12, 2022. Abstracts. 38th Annual Meeting of the American Society for Gravitational and Space Research, Houston, TX, November 9-12, 2022. , Nov-2022
Articles in Peer-reviewed Journals	Rosa-Caldwell ME, Mortreux M, Wadhwa A, Kaiser UB, Sung DM, Bouxsein ML, Rutkove SB. "Influence of gonadectomy on muscle health in micro- and partial-gravity environments in rats." J Appl Physiol (1985). 2023 May 23. https://doi.org/10.1152/japplphysiol.00023.2023 ; PMID: 37102698; PMCID: PMC10228673 , May-2023
Articles in Peer-reviewed Journals	Swain P, Mortreux M, Laws JM, Kyriacou H, De Martino E, Winnard A, Caplan N. "Skeletal muscle deconditioning during partial weight-bearing in rodents – A systematic review and meta-analysis." Life Sci Space Res. 2022 Aug;34:68-86. Review. https://doi.org/10.1016/j.lssr.2022.06.007 , Aug-2022
Articles in Peer-reviewed Journals	Swain P, Mortreux M, Laws JM, Kyriacou H, De Martino E, Winnard A, Caplan N. "Bone deconditioning during partial weight-bearing in rodents – A systematic review and meta-analysis." Life Sci Space Res. 2022 Aug;34:87-103. Review. https://doi.org/10.1016/j.lssr.2022.07.003 ; PMID: 35940692 , Aug-2022

Articles in Peer-reviewed Journals	Rosa-Caldwell ME, Mortreux M, Wadhwa A, Kaiser UB, Sung D-M, Bouxsein ML, Rutkove SB. "Sex differences in muscle health in simulated micro- and partial-gravity environments in rats." Sports Med Health Sci. 2023 Sep 12. Onine ahead of print. https://doi.org/10.1016/j.smhs.2023.09.002 , Sep-2023
Articles in Peer-reviewed Journals	Issertine M, Rosa-Calwell ME, Sung DM, Bouxsein ML, Rutkove SB, Mortreux M. "Adaptation to full weight-bearing following disuse in rats: The impact of biological sex on musculoskeletal recovery." Physiol Rep. 2024 Feb 21;12(4):e15938. https://doi.org/10.14814/phy2.15938 ; PMID: 38383049; PMCID: PMC10881285 , Feb-2024