Fiscal Year:	FY 2024	**Task Last Updated:**	FY 01/30/2024
PI Name:	Bouxsein, Mary Ph.D.		
Project Title:	Dose-Response Study of Musculoskeletal Outcomes Following Centrifugation in Adult Mice on ISS		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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) **Muscle**:Risk of Impaired Performance Due to Reduced Muscle Size, Strength and Endurance (3) **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:	Boston	**State:**	MA
Zip Code:	02215-5400	**Congressional District:**	7
Comments:			
Project Type:	FLIGHT,GROUND	**Solicitation / Funding Source:**	2017-2018 HERO 80JSC017N0001-BPBA Topics in Biological, Physiological, and Behavioral Adaptations to Spaceflight. Appendix C
Start Date:	02/14/2019	**End Date:**	06/01/2024
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	3	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
Contact Monitor:	Stenger, Michael	**Contact Phone:**	281-483-1311
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Flight Program:	ISS		
Flight Assignment:	NOTE: End date changed to 06/01/2024 per NSSC information (Ed., 11/25/22) NOTE: End date changed to 12/31/2022 per NSSC information (Ed., 2/8/22) NOTE: End date changed to 12/31/2021 per NSSC information (Ed., 4/7/21) NOTE: End date changed to 12/15/2020 per NSSC information (Ed., 7/24/20)20)		
Key Personnel Changes/Previous PI:	Additional note, per the PI: Co-Investigator Charles Farber, Ph.D. has left the project (Ed., 2/15/23). November 2020 report: Marc Wein, MD, PhD has been added as a co-investigator due to his expertise in mechanobiology and multi-omic analyses.		

COI Name (Institution):	Ferguson, Virginia Ph.D. (University of Colorado, Boulder) Rutkove, Seward M.D. (Beth Israel Deaconess Medical Center, Inc./Harvard Medical School) Willey, Jeffrey Ph.D. (Wake Forest University) Wein, Marc M.D., Ph.D. (Masachusetts General Hospital)
Grant/Contract No.:	80NSSC19K0534
Performance Goal No.:	
Performance Goal Text:	
Task Description:	Mechanical loading is required for maintenance of the musculoskeletal system. Thus, exposure to spaceflight or reduced mechanical loading on Earth induces marked bone loss, muscle atrophy, and degradation of soft-tissue structures in both the knee (e.g., cartilage, menisci, and ligaments) and hip (e.g., cartilage) joints. This is a major concern for astronauts during and after long-duration spaceflight, as they may be at increased risk for reduced performance, bone fractures, and both early-onset osteoporosis and arthritis. Artificial gravity, generated by centrifugal force generation, is a possible approach to mitigate these deleterious changes. Yet, the ability of partial gravity induced by centrifugal acceleration to inhibit adverse musculoskeletal changes in spaceflight remains unknown. Given the constraints of studying centrifugation as a countermeasure on Earth, spaceflight-based studies are needed. We propose to determine the effects of varying partial gravity levels on bone, muscle, and soft tissues of the hip and knee joints in adult mice flown aboard the International Space Station (ISS) in the Japan Aerospace Exploration Agency (JAXA) Mouse Habitat Unit. We will examine bone structure post-flight using high-resolution microcomputed tomography (microCT); bone cellularity using quantitative histomorphometry; bone function via biomechanical testing; and bone composition via Raman spectroscopy and quantitative backscattered electron imaging. We will examine neuromuscular function via pre- and post-flight gait analysis, balance beam walking, and grip strength measurements. Post-flight muscle analyses will include histology and electrical impedance myography. Post-flight analyses of joint soft-tissues will include structural measurements of cartilage, menisci, and ligaments using both contrast-enhanced high-resolution microCT and histology; molecular composition of cartilage and menisci using proteomics and Raman spectroscopy; and biomechanical properties of cartilage using nano-indentation. Cellular and molecular responses for bone, muscle, and joint soft tissues will also be evaluated via whole transcriptome analyses (e.g., RNASeq). Results from these integrated, comprehensive analyses will provide information regarding whether partial gravity, either induced by centrifugal acceleration or via Moon or Mars environments, will protect from musculoskeletal deterioration during spaceflight, or whether additional countermeasures will be necessary.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	A better understanding of the effects of different levels of mechanical loading via centrifugation on the musculoskeletal system may inform interventions and rehabilitation protocols for individuals exposed to chronic immobilization or unloading.
Task Progress:	Artificial gravity (AG) by centrifugation is a potential countermeasure to mitigate deleterious musculoskeletal changes associated with microgravity (µG). Prior work showed that exposure to 1G by artificial gravity inhibited musculoskeletal deterioration associated with spaceflight (Shiba et al., 2017). Yet, the responses of the musculoskeletal system to varied magnitudes of AG are not known. To address this knowledge gap, an interdisciplinary project team of investigators, from the US and from Japan, designed an integrated protocol to assess the effects of varied levels of artificial gravity on various physiologic systems. Our team focused on the musculoskeletal system. Adult (12 weeks) male C57Bl/6J mice were exposed to either microgravity alone (0G), or to 0.33G, 0.67G, or 1G via centrifugation using the Japan Aerospace Exploration Agency (JAXA) Multiple Artificial-gravity Research System (MARS) during the Joint Partial-Gravity Rodent Research (JPG-RR)/Mouse Habitat Unit 8 (MHU-8) 30-day mission on the International Space Station (n=5-6/group). Ground controls were housed in an identical environment (HGC, n=12). The launch occurred in March 2023, with a successful live animal return in April 2023. Prior to launch and shortly after live animal return, we assessed gait performance, grip strength, bone mass and body composition. Bone and muscle tissues were harvested at necropsy for morphologic and transcriptomic analyses (via bulk RNASeq). In addition, we collected blood cell-depleted femoral bone marrow (n=5-6/group) postflight in the 0G and 1G groups for single-cell RNA sequencing using the Highly Integrated Virtual Environment (HIVE) platform (Honeycomb). Preliminary results indicate that artificial gravity was able to fully- or partially-mitigate deleterious effects of microgravity on the musculoskeletal system, including gait performance, bone mass and microstructure, and muscle morphology. Further, for the first time, we successfully collected spaceflight-flown specimens for analysis by single-cell RNA sequencing (RNASeq).
Bibliography Type:	Description: (Last Updated: 02/21/2024)
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Abstracts for Journals and Proceedings	Coulombe J, Wadhwa A, Mortreux M, Emerzian S, Ciola J, Chow J, Brooks D, Willey J, Fuller C, Takahashi S, Hotz-Vitaterna M, Bouxsein ML. "Response of the murine musculoskeletal system to artificial gravity induced by centrifugation on the International Space Station: A NASA-JAXA collaboration. " ASBMR 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023. Abstracts. ASBMR 2023 Annual Meeting, Vancouver, BC, Canada, October 13-16, 2023. Poster. , Oct-2023
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