Fiscal Year:	FY 2022	**Task Last Updated:**	FY 12/13/2021
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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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:**	12/31/2022
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**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 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:	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):	Farber, Charles Ph.D. (University of Virginia, Charlottesville) 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. (Massachusetts 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:	Spaceflight exposes physiologic systems to multiple stressors, including radiation, confinement, and lack of gravitational loading. Artificial gravity by centrifugation has been proposed as a potential countermeasure to mitigate physiologic changes due to lack of gravitational loading. Indeed, Shiba et al. (Sci Report 2017) reported that exposure of male mice to artificial gravity (at 1G) by centrifugation for 35 days on the ISS prevented deleterious musculoskeletal changes associated with microgravity. Yet, the physiologic responses to lesser magnitudes of artificial gravity are not well established. Thus, the aim of this multi-Principal Investigator (PI), multi-national collaborative study is to determine how different physiologic systems respond to various levels of partial gravity. Using the JAXA Multiple Artificial-gravity research system (MARS), adult male C57Bl/6 mice (age 12 weeks) will be exposed to either 0G, 0.33G, 0.67G, or 1G (6 mice per group) during a 30-day missing to the International Space Station. Two groups of ground controls will be utilized: one group (n=12) will be housed in identical environment as the artificial gravity cages and a second group (n=12) will be housed in normal cages in the NASA vivarium. All mice will be returned to Earth alive. Prior to launch, mice will undergo implantation of an intraperitoneal datalogger that continuously records body temperature for evaluation of circadian rhythms. Mice will also undergo a series of preflight testing, including muscle function (via grip strength), neuromotor function via gait analysis and rotarod testing, and assessment of bone mass and body composition via DXA. Fecal pellets will be collected for microbiome analyses. During flight, mice will be weighed and fecal pellets collected weekly in coordination with cage maintenance activities. Injection of fluorochromes towards the end of the flight period will facilitate assessment of bone formation rate via histomorphometry. Upon return, mice will repeat muscle function and neuromotor testing, and then tissues will be collected by each principal investigator for a variety of histologic, transcriptomic and proteomic analyses. It is expected the flight for this experiment will occur in Feb 2023. Project Accomplishments Study Protocol & Administrative Tasks. We have worked with the multi-PI team to create a harmonized protocol that is able to complete the scientific aims of each individual PI. The PI team has met monthly. We reviewed, edited, and approved the Science Requirements Document. We attended a kick-off meeting with the service provider, Leidos. Ground-based Test of Fluorochrome Labels. The primary aim of this technical experiment was to determine if the fluorophores would be stable and taken up in the bone if prepared and frozen for 5 weeks and then injected into the animals. We also tested different combinations of fluorophores (Calcein green, Calcein Blue, Alizarin red, and Xylenol orange). In addition, we collected fecal samples and soleus muscle tissue for Mouse Habitat Unit (MHU) MHU-8 co-principal investigators M. Vitaterna and S. Takahashi, respectively, to determine whether the fluorochrome injections impacted their proposed outcomes. Reference: Shiba D, Mizuno H, Yumoto A, Shimomura M, Kobayashi H, Morita H, Shimbo M, Hamada M, Kudo T, Shinohara M, Asahara H, Shirakawa M, Takahashi S. Development of new experimental platform 'MARS'-Multiple Artificial-gravity Research System-to elucidate the impacts of micro/partial gravity on mice. Sci Rep. 2017 Sep 7;7(1):10837.
Bibliography Type:	Description: (Last Updated: 02/21/2024)