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| **Fiscal Year:** | FY 2023 | **Task Last Updated:** | FY 12/08/2022 |
| **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<br>(2) **Muscle**:Risk of Impaired Performance Due to Reduced Muscle Size, Strength and Endurance<br>(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:** | 06/01/2024 |
| **No. of Post Docs:** | 1 | **No. of PhD Degrees:** | |
| **No. of PhD Candidates:** | 2 | **No. of Master' Degrees:** | |
| **No. of Master's Candidates:** | | **No. of Bachelor's Degrees:** | |
| **No. of Bachelor's Candidates:** | 1 | **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)<br>NOTE: End date changed to 12/31/2022 per NSSC information (Ed., 2/8/22)<br>NOTE: End date changed to 12/31/2021 per NSSC information (Ed., 4/7/21)<br>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. | | |

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| **COI Name (Institution):** | Ferguson, Virginia Ph.D. ( University of Colorado, Boulder )<br>Rutkove, Seward M.D. ( Beth Israel Deaconess Medical Center, Inc./Harvard Medical School )<br>Willey, Jeffrey Ph.D. ( Wake Forest University )<br>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:** | 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 NASA-PI team and JAXA-team have met twice a month. We reviewed, edited, and approved the Science Requirements Document (SRD), Investigator Summer Form (ISF), the Science Requirements and Operations Document (SORD), the IACUC Application, and the PSRD documents.<br>We have worked extensively with the project team to revise the dissection schedule to better accommodate our scientific needs. Our team attended Radiation Safety Training sponsored by Kennedy Space Center (KSC) and completed paperwork to gain approval to be able to use an X-ray generating device at KSC.<br><br>Ground-based Tests: DXA device testing (completed in 2022) We compared the accuracy and precision of a new peripheral dual-energy X-ray absorptiometry (DXA) device for rodents, the InAlyzer, to that of an established device, the PIXImus. We measured bone mass and body composition of 18 male C57Bl/6J mice (6 each of ages 8, 14, and 24 weeks) on the two DXA devices. We compared the body composition measurements to those from whole-body magnetic resonance imaging (MRI), taken to be the gold standard. We found that the accuracy and precision of InAlyzer measurements were comparable to those from the PIXImus. Short-term precision was excellent for both devices, ranging between 0.39 and 2.4%. Given the safety and efficiency advantages of the InAlyzer device, we recommend that it be used for pre- and post-flight measurements in the MHU-8 mission. Further details are provided in the Technical Report submitted to the Project Team.<br><br>Ground-based Tests: Fluorochrome labels (completed in 2021) We previously reported the results of the ground-based test designed 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 used adult C57/Bl6J mice to test different combinations of fluorophores (Calcein green, Calcein Blue, Alizarin red, and Xylenol orange). In addition, we collected fecal samples and soleus muscle tissue for MHU-8 co-principal investigators M. Vitaterna and S. Takahashi, respectively, to determine whether the fluorochrome injections impacted their proposed outcomes. We found that calcein green, followed by alizarin red, demonstrated strong and clear labeling with both the fresh and frozen fluorophores preparations. There were no differences between the mice injected with PBS, or the fluorochromes, with both showing weight gain over time. In addition, Dr. Satoro Takahashi reported that there were no differences in gene expression in the soleus muscle when comparing mice injected with fluorochromes vs. those injected with PBS and Dr. Hotz-Vitaterna reported no impact of fluorochrome injections on the microbiome. We conclude that preparing the fluorophores and syringes ~5 weeks ahead and freezing at -80°C until the injections on orbit will be acceptable for dynamic histomorphometry measurements and do not interfere with other scientific objectives proposed in this study. We plan to use calcein green and alizarin red as these give the best images. |
| **Bibliography Type:** | Description: (Last Updated: 02/21/2024) |