Fiscal Year:	FY 2019	**Task Last Updated:**	FY 08/30/2018
PI Name:	Willey, Jeffrey S. Ph.D.		
Project Title:	Exercise Countermeasures for Knee and Hip Joint Degradation during Spaceflight		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	SPACE BIOLOGY--Developmental biology		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	(1) Cell & Molecular Biology (2) Animal Biology: Vertebrate		
Space Biology Cross-Element Discipline:	(1) Musculoskeletal Biology		
Space Biology Special Category:	(1) Translational (Countermeasure) Potential		
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Zip Code:	27157-0001	**Congressional District:**	5
Comments:	NOTE: PI formerly at Clemson University when NSBRI Postdoctoral Fellow Feb 2008-Oct 2010 (Ed., 12/18/2014)		
Project Type:	Flight	**Solicitation / Funding Source:**	2014 Space Biology Flight NNH14ZTT001N
Start Date:	10/28/2014	**End Date:**	03/31/2020
No. of Post Docs:		**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:		**Monitoring Center:**	NASA ARC
Contact Monitor:	Sato, Kevin	**Contact Phone:**	650-604-1104
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Flight Program:	ISS		
Flight Assignment:	ISS Rodent Research-9 NOTE: End date changed to 3/31/2020 per F. Hernandez/ARC (Ed., 6/23/17)		
Key Personnel Changes/Previous PI:	August 2017 report: Dr. Ted Bateman added as CoInvestigator as of July 2017.		
COI Name (Institution):	Smith, Thomas Ph.D. (Wake Forest University Health Sciences) Bateman, Ted Ph.D. (University of North Carolina Chapel Hill)		
Grant/Contract No.:	NNX15AB50G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Maintaining musculoskeletal health during long-duration spaceflight is crucial for ensuring both mission success and full skeletal recovery upon returning to weight-bearing. Clinical and preclinical evidence indicates that cartilage degradation in the hip and knee joints occurs with reduced weight-bearing. Less well characterized are the damaging effects of spaceflight-relevant radiation on cartilage, including exposure to solar particle events (SPE). Deterioration of the hip and knee joint during prolonged spaceflight has the potential to reduce an astronaut's performance during a mission, cause arthritis, and negatively impact the astronaut's long-term quality of life (QOL). Our study will test the hypothesis that mouse hip and knee joints exposed to microgravity on the International Space Station (ISS) or from reduced weight bearing via tail-suspended with or without exposure to spaceflight-relevant doses of radiation in Definition Phase studies will exhibit profound tissue degradation. Additionally, this degradation can be recovered using aerobic (running) and resistance (climbing) exercise countermeasures. To study these problems, we will determine the hip and knee joint damage that occurs in mice that will fly in space on the International Space Station for 30 days. This damage will be compared to the hip and knee joint damage in another group of mice kept on Earth that also will not have weight on the hip and knee joints for 30 days, with or without receiving radiation exposure that simulates a solar flare. Damage to the hip and knee joint structures will be determined using imaging techniques, engineering devices to measure tissue strength, stained tissue sections, and identification of the molecules that cause the damage. The ability to walk normally after 30 days of weightlessness will also be determined. Finally, we will determine if treadmill running or climbing can reverse any of the hip and knee joint damage caused by being in the weightless space environment. Our goal is to determine, 1] if hip and knee joint damage occurs in the weightless space environment, and 2] if recovery from this damage is possible with exercise.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	From these studies, we also will gain insights into how arthritis and joint failure develop in both patients that receive radiation therapy for the treatment for cancer, and in patients with limited mobility (cancer patients, wheel-chair bound spinal cord injury patients, or after limb surgery), and how it can be prevented.
Task Progress:	1. We finished all the tail suspension +/- simulated spaceflight radiation studies and have submitted a paper for publication. Mice were either hindlimb unloaded (HLU) (n=40) or remained full weight-bearing as Ground mice (n=40). Within each of these groups, mice either received no radiation, or 1 of 3 low-dose, spaceflight-relevant radiation scenarios. We measured cartilage and joint damage on Day 30 after initiating HLU. Primary Results: Contrast-enhanced microCT demonstrated decreased in volume and thickness at the site of primary weight-bearing in the knee (e.g., the femoral-tibial cartilage-cartilage contact point) in all treatment groups vs. GROUND-SHAM. Interestingly and importantly, damage was localized to the sites of most weight bearing; cartilage is senstiive to loading. Within the knee cartilage, the protein collagen was reduced, and collagen type II-degrading matrix metalloproteinase-13 (MMP-13) were greater in all groups vs. controls indicating that cartilage degraded after both radiation and reduced weight bearing. Circulating serum cartilage oligomeric matrix proteins (sCOMP), biomarker for ongoing cartilage degradation, was increased in all of the irradiated groups vs. GROUND-SHAM, regardless of unloading. Mass spectrometry, combined with Ingenuity Pathway Analysis (IPA), of the cartilage lining the femoral head showed decrease in cartilage compositional proteins, increased osteoarthritic pathways, and decreased cell survival by increased apoptosis and oxidative stress. Our findings demonstrate that both individually and combined HLU and spaceflight-relevant doses of irradiation lead to cartilage degradation of the knee and hip with expression of an arthritic phenotype. Moreover, early administration of low dose irradiation (0.1 Gy, 0.5 Gy, or 1 Gy) causes an active catabolic response in cartilage 24 days post irradiation. IMp 2. Flight study: Our mouse payload has been launched aboard the SpaceX-12 mission to the International Space Station. We successfully brought our Digigait treadmill down to the Kennedy Space Center, performed an initial gait assessment on all mice; grouped the mice; and after launch collected the baseline tissues for ourselves and for biospecimen sharing program (BSP). We traveled to Loma Linda University, where we repeated the gait assessment on the flight animals upon return, a new Cohort Control group of mice, and again collected tissues for our primary science and for BSP. We have analyzed how gait is altered post flight. Analysis of tissues is ongoing. Primary results: Gait data were acquired over ~1.5 minutes/mouse. Several patterns of gait changes were noted post-flight. Stride width variance increased in both forelimbs ($p<0.05$) and hind limbs ($p<0.001$), indicating an increased risk of falling. Increased swing phase duration observed in the hind limbs post-flight ($p < 0.05$) characterizes an arthritic gait. Step angle widened in hind limbs post-flight, suggesting impaired CNS motor centers with ataxia ($p < 0.01$). Paw area variability at peak stance increased in hind limbs ($p < 0.01$), reflecting impaired neuromotor control. Importantly, while many gait patterns indicated neuromotor deficits, most remained unaltered. Our data indicates that longitudinal gait analysis of rodents provides a non-invasive assay to measure functional responses to spaceflight. The mobile DigiGait system permits identification of gait changes in rodents suggestive of functional impairment. The majority of deficits from RR-9 mice were noted as sensorimotor in nature. Deficits were more pronounced in hind limbs vs. forelimbs, which could be related to locomotor habits in the Rodent Habitats on ISS (e.g., grabbing wire mesh).
Bibliography Type:	Description: (Last Updated: 01/22/2025)
Abstracts for Journals and Proceedings	Kwok A, Moore JE, Collins B, Pecaut M, Nishiyama N, Mao XW, Willey JS. "Knee and Hip Joint Damage from Reduced Weight-Bearing and/or Spaceflight Radiation. Knee and Hip Joint Damage from Reduced Weight-Bearing and/or Spaceflight Radiation." Session: LS Systems V: Musculoskeletal System II - Bone. Presented at 33rd Annual Meeting of the American Society for Gravitational and Space Research, Seattle, WA, October 25-28, 2017. 33rd Annual Meeting of the American Society for Gravitational and Space Research, Seattle, WA, October 25-28, 2017. , Oct-2017
Abstracts for Journals and Proceedings	Mao XW, Nishiyama N, Pecaut M, Willey JS. "Retinal oxidative damage in low-dose radiated and hindlimb unloaded mice." Poster. 33rd Annual Meeting of the American Society for Gravitational and Space Research, Seattle, WA, October 25-28, 2017. 33rd Annual Meeting of the American Society for Gravitational and Space Research, Seattle, WA, October 25-28, 2017. , Oct-2017

Abstracts for Journals and Proceedings	Willey JS, Kwok A, Moore JE, Mao XW, Collins BE. "Knee And Hip Joint Degradation from Reduced Weight-Bearing and/or Low-Dose Radiation." Rodent models. 2018 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2018. 2018 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2018. , Jan-2018
Articles in Peer-reviewed Journals	Farris M, McTyre ER, Okoukoni C, Dugan G, Johnson BJ, Blackstock AW, Munley MT, Bourland JD, Cline JM, Willey JS. "Cortical thinning and structural bone changes in non-human primates after single-fraction whole-chest irradiation." Radiat Res. 2018 Jul;190(1):63-71. Epub 2018 May 8. https://doi.org/10.1667/RR15007.1 ; PubMed PMID: 29738279; PubMed Central PMCID: PMC6036641 , Jul-2018