Fiscal Year:	FY 2020	**Task Last Updated:**	FY 08/29/2019
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:**	03/31/2021
No. of Post Docs:		**No. of PhD Degrees:**	
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA ARC
Contact Monitor:	Griko, Yuri	**Contact Phone:**	650-604-0519
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Flight Program:	ISS		
Flight Assignment:	ISS Rodent Research-9 NOTE: End date changed to 3/31/2021 per F. Hernandez/ARC (Ed., 4/7/2020) NOTE: End date changed to 3/31/2020 per F. Hernandez/ARC (Ed., 6/23/17)		
Key Personnel Changes/Previous PI:	August 2019 report: Dr. Ted Bateman added as CoInvestigator as of July 2017, and continued until April 2018. Dr. Tom Smith retired in 2018 and is no longer CoInvestigator on the project.		
COI Name (Institution):	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 this can be prevented.
Task Progress:	Summary of Progress to Date We have met 3 main milestones during the past year. i] We have completed the ground-based Definition Phase portion for Specific Aim 1 and have published that portion in the journal Radiation Research, which examines the combined effect of reduced weight-bearing (HLU--hindlimb unloading) with/without exposure to one of 3 low dose radiation scenarios (0.1, 0.5, or 1 Gy) in regards to whole joint health. ii] We have completed the flight experiment. The data from the gait assessment has been submitted for publication; we have resubmitted our revisions. iii] Additionally, we have finished analyzing the spaceflight data and have started writing up a publication (combining these results with results from STS-135). Progress to date includes: A. Results from Specific Aim 1 Definition Phase – a ground based study in which we examined the individual and combined effects of low dose radiation and reduced weight bearing via tail suspension in mice: Both reduced weight bearing and low dose radiation as independent challenges cause degradation of knee cartilage and increases arthritic, catabolic signaling pathways in cartilage that can lead to arthritis. B. Flight study RR-9: Our mouse payload has been launched as part of the Rodent Research-9 mission aboard SpaceX-12 to the International Space Station. Our two primary aims were to examine if knee joint degradation (e.g., articular cartilage and menisci) occurred after spaceflight; and if gait alterations occurred that could indicate pathology in the joint or otherwise. B1. Knee joint findings. Articular cartilage volume lining the medial tibial plateau in FLIGHT mice measured from microCT was significantly lower than controls. Cartilage thinning was localized to the weight-bearing tibial-femoral contact point, which is the point of the greatest weight bearing within the knee. Thus loss of cartilage was greatest where the loading is the generally the greatest -- reducing pressure across the knee during flight had the biggest negative impact at that location. Within the knee cartilage, enzymes capable of breaking down cartilage (MMPs) were increased in the spaceflight FLIGHT cartilage. Additionally, the molecules that provide the spongy, compressive properties of cartilage were lower after spaceflight. The meniscus is a tissue in the knee that stabilizes the structure. We found that Meniscal volume was significantly lower than controls after flight. Additionally, the same molecules (proteoglycans) that provide the compressive properties in cartilage were also lower in the menisci of FLIGHT mice. This pattern was similar to results from the STS-135 space shuttle flight flight, in which proteoglycans were lower in menisci from left (-11%; $p<0.05$) and right (-9%; $p=.1$) knees vs controls. We also found that within the menisci, the "control pathways" that can lead to damage or arthritis were activated, specifically ones that can result in a decrease in meniscal volume. Many proteins associated with building new cartilage and meniscal tissues were lower after flight, and this could be due to lowered defenses against free radicals. SUMMARY: Degradation of knee soft tissues occurred after flights on ISS. Cartilage loss localized to the highest weight-bearing location across the knees. Excess oxidative stress is a known cause for meniscal and cartilage degradation; our data indicate this as potentially a contributor to the observed joint degradation. B2. Gait Assessment Findings. We have submitted our gait For FLIGHT mice; many of the evaluated gait characteristics in the hind limbs were significantly changed, including: stride width variability; stride length and variance; stride, swing, and stance duration; paw angle and area at peak stance; and step angle, among others. Gait characteristics that decreased included stride frequency, and others. Moreover, numerous forelimb gait characteristics in the FLIGHT mice were changed at post-flight measures relative to pre-flight. We also sought to identify gait alterations that are reflective of joint (cartilage) degradation, a known response of knees to reduced weight bearing. Some patterns of gait change in rodents reflect musculoskeletal deficits, a well-described consequence of prolonged periods of reduced weight bearing in mice. For instance, an arthritic gait in rodents may display increased stride duration and reduced stride length and/or increased stride width, with related pain. Increased stride duration was observed in the flight animals, but as noted the stride length was significantly increased and stride width was unaltered, which is in contrast to what one might expect with painful arthritis. Thus while cartilage degradation was noted from anatomic and proteomic assessment, the reponse may not be painful at the point of tissue harvest.

	B3. Muscle Metabolomic findings. We examined how metabolism was changed in the gastrocnemius, and the quadriceps femoris (“quadriceps”) muscles, and was conducted at Georgetown University by Dr. Willey’s collaborator, Dr. Lia Laiakis. Results demonstrate the increased responsiveness of gastrocnemius to spaceflight compared to quadricep in the metabolomic level. All the data suggest that microgravity and spaceflight have a direct effect on the metabolomic profiles of muscle tissues. However, some muscles appear to be more responsive compared to others, or some have the ability to reprogram efficiently upon return to Earth.
Bibliography Type:	Description: (Last Updated: 04/06/2023)
Abstracts for Journals and Proceedings	Mao XW, Nishiyama NC, Willey JS, Delp M, Pecaut MJ. "Acute effect of spaceflight on ocular structure, intraocular pressure and retina." Podium. 34th Annual Meeting of the American Society for Gravitational and Space Biology, Bethesda, MD, October 31-November 3, 2018. ASGSR Program Book. 34th Annual Meeting of the American Society for Gravitational and Space Biology, Bethesda, MD, October 31-November 3, 2018. , Oct-2018
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