Fiscal Year:	FY 2021	**Task Last Updated:**	FY 09/16/2021
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		
PI Email:	jwilley@wakehealth.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	336-713-7637
Organization Name:	Wake Forest University		
PI Address 1:	Radiation Biology Section		
PI Address 2:	Medical Center Blvd, 4th Floor NRC Building		
PI Web Page:			
City:	Winston-Salem	**State:**	NC
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:**	05/31/2021
No. of Post Docs:		**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**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
Contact Email:	Yuri.V.Griko@nasa.gov		
Flight Program:	ISS		
Flight Assignment:	ISS Rodent Research-9 NOTE: End date changed to 5/31/2021 per F. Hernandez/ARC and NSSC information (Ed., 5/5/21) 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:	NOTE September 2021: Dr. Ted Bateman was no longer a CoI during the last year of the project, from September 2020-May 2021.		
COI Name (Institution):			
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:	FINAL REPORTING SEPTEMBER 2021 With a return to lab from COVID restrictions, we compiled and wrote a manuscript that incorporated all the finished data from our ISS mission, together with the parallel ground-based tail suspension study (with and without a readaptation period that included exercise interventions or not), and also included data from knee joint degradation that were collected during the final Space Shuttle mission (STS-135). Our final conclusion was that spaceflight and reduced weight-bearing on the ground induce an arthritic response in the knees of mice, which can be reversed with a return to weight-bearing (after hindlimb unloading-HLU) if exercise is performed. This final paper was submitted to Scientific Reports and published in the fall. Moreover, the student who was working on the project as his dissertation research, Andy Kwok, wrote and defended his dissertation in Spring, 2021. [Ed. note: see Bibliography section for noted publications] ANNUAL REPORTING SEPTEMBER 2020 We examined if reduced weight bearing on Earth using a hindlimb unloading (HU) model could cause damage to menisci and cartilage, as during spaceflight. What we found was that in male and female mice, the degree of cartilage and meniscus damage was similar to what was observed after 30 days in space, and occurred at the same location (the region in the knee that supports most of the weight versus gravity). Thus cartilage degradation, and meniscal loss, occurs with reduced weight bearing, and HU is a good analogue for joint damage that occurs during spaceflight. We then identified that both running and climbing exercise can in part mitigate the damage to cartilage and menisci that is caused by reduced weight bearing.
Bibliography Type:	Description: (Last Updated: 04/06/2023)
Abstracts for Journals and Proceedings	Willey JS. "Radiation and reduced weight bearing as combined skeletal hazards during spaceflight." Symposium titled "Space, We are Going." 65th Annual Meeting of the Radiation Research Society, San Diego, CA, November 3-6, 2019. Abstract book. 65th Annual Meeting of the Radiation Research Society, San Diego, CA, November 3-6, 2019. , Nov-2019
Abstracts for Journals and Proceedings	Kwok A, Rosas S, Bateman TA, Livingston EW, Moore JE, Bouxsein M, Ferguson VL, Stodieck L, Zawieja DC, Mao XW, Delp MD, Willey JS. "Damage to the Menisci and/or Knee Articular Cartilage in Mice after Spaceflight: RR-9 and STS-135 Results." 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. Abstract Book. 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. , Nov-2019
Abstracts for Journals and Proceedings	Mao XW, Nishiyama NC, Stanbouly S, Pecaut MJ, Willey JS, Zawieja DC, Delp M. "Spaceflight impacts on neurovascular remodeling and BBB integrity." 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. Abstract Book. 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. , Nov-2019
Abstracts for Journals and Proceedings	Overbey EG, da Silveira WA, Stanbouly S, Nishiyama NC, Pecaut MJ, Zawieja DC, Wang C, Willey JS, Delp MD, Mao XW. "Spaceflight influences gene expression, photoreceptor integrity, and oxidative stress-related damage in the murine retina." 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. Abstract Book. 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. , Nov-2019

Abstracts for Journals and Proceedings	da Silveira WA, Fazelinia H, Rosenthal SB, Laiakis EC, Meydan C, Foox J, Kidane Y, Rathi KS, Smith SM, Zanello SB, Crucian B, Wang D, Nugent A, Zwart SR, Schrepfeer S, Singh LN, Wallace D, Willey J, Costa H, McDonald JR, Costes SV, Mason C, Fisch K, Taylor D, Hardiman G, Beheshti A. "Mitochondrial driven metabolic alterations inferred from GeneLab database as mediators of spaceflight health risks." 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. Abstract Book. 35th Annual Meeting of the American Society for Gravitational and Space Research, Denver, CO, November 20-23, 2019. , Nov-2019
Abstracts for Journals and Proceedings	Kwok A, Rosas S, Bateman TA, Livingston EW, Moore JE, Bouxsein M, Ferguson VL, Stodieck L, Yammani YR, Kerr BE, Zawieja DC, Mao XW, Delp MD, Willey JS. "Damage to menisci and/or knee articular cartilage in male and female mice after spaceflight: RR-9, STS-135, and ground-based hind limb unloading results." 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. Abstract Book [#20330]. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020
Abstracts for Journals and Proceedings	Laiakis E, Delp M, Zawieja D, Mao X, Livingston E, Bateman T, Willey JS. "Metabolomic alterations associated with spaceflight and microgravity in gastrocnemius and quadriceps ." 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. Abstract Book. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020
Abstracts for Journals and Proceedings	Mitchell R, Frederick N, Tarasova O, Kiryukhina O, Tansey P, Holzman E, Mao X, Willey JS, Zawieja D, Delp M, Bagher P. "Effects of spaceflight on murine basilar arteries." 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. Abstract Book #20360. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020
Abstracts for Journals and Proceedings	Willey JS, Kwok AT, Miles LA, Moore J, Mao XM, Wallace RW, Floyd MC, Aunon-Chancellor S. "Alpha Klotho is Reduced After Spaceflight and Reduced Weight-bearing Models: Implications As a Novel Biomarker for Bone and/or Renal Dysfunction During Spaceflight." 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. Abstracts. 36th Annual Meeting of the American Society for Gravitational and Space Research, Virtual Meeting, November 5-6, 2020. , Nov-2020
Abstracts for Journals and Proceedings	Willey JS, Kwok AT, Miles LRosas S, Bateman TA, Livingston E, Moore JE, Yammani R, Kerr BA, Plate FJ, Zawieja DC, Mao XM, Delp MD. "Spaceflight and reduced weight-bearing on Earth damages knee articular cartilage and menisci." 2021 Orthopedic Research Society, Virtual, February 12-16, 2021. Abstracts. 2021 Orthopedic Research Society, Virtual, February 12-16, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Kwok A, Rosas S, Bateman TA, Livingston EW, Smith TL, Moore JE, Zawieja DC, Hampton T, Mao XW, Delp MD, Willey JS. "Altered rodent gait characteristics after ~35 days in orbit aboard the International Space Station." Life Sci Space Res (Amst). 2020 Feb;24:9-17. https://doi.org/10.1016/j.lssr.2019.10.010 ; PMID: 31987483 , Feb-2020
Articles in Peer-reviewed Journals	Overbey EG, da Silveira WA, Stanbouly S, Nishiyama NC, Roque-Torres GD, Pecaut MJ, Zawieja DC, Wang C, Willey JS, Delp MD, Hardiman G, Mao XW. "Spaceflight influences gene expression, photoreceptor integrity, and oxidative stress-related damage in the murine retina." Sci Rep. 2019 Sep 16;9(1):13304. https://doi.org/10.1038/s41598-019-49453-x ; PMID: 31527661; PMCID: PMC6746706 , Sep-2019
Articles in Peer-reviewed Journals	Willey JS, Auñón-Chancellor S, Miles LA, Moore JE, Mao XW, Wallace RW, Foy MC. "aKlotho decreases after reduced weight-bearing from both spaceflight and hindlimb unloading." npj Microgravity. 2022 Jun 2;8:18. https://doi.org/10.1038/s41526-022-00203-w ; PMID: 35654945; PMCID: PMC9163032 , Jun-2022
Articles in Peer-reviewed Journals	Kwok AT, Mohamed NS, Plate JF, Yammani RR, Rosas S, Bateman TA, Livingston E, Moore JE, Kerr BA, Lee J, Furdui CM, Tan L, Bouxsein ML, Ferguson VL, Stodieck LS, Zawieja DC, Delp MD, Mao XW, Willey JS. "Spaceflight and hind limb unloading induces an arthritic phenotype in knee articular cartilage and menisci of rodents." Sci Rep. 2021 May 18;11(1):10469. https://doi.org/10.1038/s41598-021-90010-2 ; PMID: 34006989; PMCID: PMC8131644 , May-2021
Articles in Peer-reviewed Journals	da Silveira WA, Fazelinia H, Rosenthal SB, Laiakis EC, Kim MS, Meydan C, Kidane Y, Rathi KS, Smith SM, Stear B, Ying Y, Zhang Y, Foox J, Zanello S, Crucian B, Wang D, Nugent A, Costa HA, Zwart SR, Schrepfer S, Elworth RAL, Sapoval N, Treangen T, MacKay M, Gokhale NS, Horner SM, Singh LN, Wallace DC, Willey JS, Schisler JC, Meller R, McDonald JT, Fisch KM, Hardiman G, Taylor D, Mason CE, Costes SV, Beheshti A. "Comprehensive multi-omics analysis reveals mitochondrial stress as a central biological hub for spaceflight impact." Cell. 2020 Nov 25;183(5):1185-201.e20. https://doi.org/10.1016/j.cell.2020.11.002 ; PMID: 33242417; PMCID: PMC7870178 , Nov-2020
Articles in Peer-reviewed Journals	Willey JS, Britten RA, Blaber E, Tahimic CGT, Chancellor J, Mortreux M, Sanford LD, Kubik AJ, Delp MD, Mao XW. "The individual and combined effects of spaceflight radiation and microgravity on biologic systems and functional outcomes." J Environ Sci Health C Toxicol Carcinog. 2021 Apr 27;39(2):129-79. https://doi.org/10.1080/26896583.2021.1885283 ; PMID: 33902391; PMCID: PMC8274610 , Apr-2021
Dissertations and Theses	Kwok A. "Spaceflight Effects on Joint Health and Gait." Dissertation, Wake Forest University, Spring 2021. , May-2021