Fiscal Year:	FY 2015	**Task Last Updated:**	FY 07/07/2015
PI Name:	Mellor, Liliana F. Ph.D.		
Project Title:	Induction of Early Stages of Osteoarthritis After Exposure to Microgravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Musculoskeletal Alterations Team		
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) **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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PI Organization Type:	UNIVERSITY	**Phone:**	208-426-2238
Organization Name:	North Carolina State University		
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PI Web Page:			
City:	Raleigh	**State:**	NC
Zip Code:	27695-7115	**Congressional District:**	4
Comments:	NOTE: formerly at Boise State University until fall 2013 (Ed., Jan 2014)		
Project Type:	Ground	**Solicitation / Funding Source:**	2011 NSBRI-RFA-11-01 Postdoctoral Fellowships
Start Date:	11/01/2011	**End Date:**	02/28/2015
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date change to 2/28/2015 per NSBRI (Ed., 12/2/14) NOTE: End date is now 11/30/2014 with PostDoc change in institution, per NSBRI (Ed., 1/15/14) NOTE: End date changed to 11/30/2013 per NSBRI (Ed., 10/24/13)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Loboa, Elizabeth (MENTOR/ North Carolina State University)		
Grant/Contract No.:	NCC 9-58-PF02601		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Little is known about the effects of spaceflight on articular cartilage health. Unlike bone and muscle, cartilage lacks the ability to regenerate. Once a catabolic cascade is triggered, it usually results in osteoarthritis. Some studies have shown degradation of the articular cartilage in response to unloading and prolonged bedrest. However, the underlying molecular mechanisms of articular cartilage degradation in response to unloading are still elusive. The overall goal of my research is to understand and elucidate key molecular mechanisms involved in response of cartilage to changes in gravitational forces. The majority of my focus is at the cell level, with analyses of potential approaches to translate these changes to tissue and joint level. To begin to address this problem, I investigated the effects of simulated microgravity on chondrocytes using the rotating wall vessel (RWV) bioreactor. Also, in collaboration with Dr. Jeff Willey, I studied the combined effects of radiation and simulated microgravity on articular cartilage health. I found that chondrocytes exposed to simulated microgravity undergo morphological rearrangement of the actin cytoskeleton. This change was not observed in irradiated cells; however, when cells were exposed to both radiation and simulated microgravity, they developed long stress-like fibers, resembling a more fibroblast morphology as compared to the cortical control chondrocytes. Gene expression analyses confirmed that cells exposed to both radiation and simulated microgravity express more collagen I and less collagen II and aggrecan, which is characteristic for de-differentiated chondrocytes. We also determined that irradiated chondrocytes upregulate R-spondin1. R-spondin1 is a positive regular of Wnt signaling that has been shown to protect against radiation-induced damage to the oral mucosa and intestine. R-spondin1 has also been shown to protect against inflammatory bone damage in a mouse model of arthritis. Our results are interesting given R-spondin1 is upregulated in response to radiation, but not radiation and microgravity. If chondrocytes in normal gravity respond to radiation by producing "radioprotectant" genes, simulated microgravity is inhibiting that effect, making cartilage cells more susceptible to radiation-induced damage in microgravity conditions. This data shows that microgravity may inhibit the radio-protective mechanism of chondrocytes, suggesting a combined synergistic, degradatory effect of simulated microgravity and radiation, which mimics the environment of spaceflight. The mechanisms responsible for these morphological and signal transduction changes in response to simulated microgravity and radiation are still under investigation. Another unexpected and compelling finding was that chondrocytes respond to simulated microgravity by up-regulating sclerostin, an inhibitor of Wnt signaling known to induce bone density loss in space. However, according to a recent study, sclerostin may prevent cartilage from further degradation by decreasing production of matrix degrading genes, suggesting a chondro-protective role for sclerostin in this tissue. Therapeutic treatments using an antibody against sclerostin have shown promising results to prevent bone density loss in unloading conditions. However, the effects of blocking sclerostin on neighboring tissue, such as articular cartilage have not been addressed and may have adverse effects. My goal for next year is to compare results of cells exposed to microgravity to cells incubated in hydrostatic pressure, an environment known to induce expression of anabolic genes in articular cartilage. In addition, I will investigate the role of primary cilia in microgravity, an important organelle involved in mechanotransduction that has also been associated with the Wnt signaling pathway.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Astronauts are exposed to prolonged periods of microgravity during spaceflight. Lack of gravity is known to negatively affect the musculoskeletal system, mainly bone and skeletal muscle, which are constantly exposed to mechanical loading on Earth. However, another important component of the musculoskeletal system, the synovial joint, has not been fully investigated in space-like conditions. Unlike bone and muscle, the articular cartilage of the synovial joint has limited regenerative capacity, and has a relatively slow turn over compared to the fast remodeling of bone. Cartilage degradation leads to a severe disease known as osteoarthritis (OA). OA is the leading cause of disability in the US, and one of the few chronic diseases of aging without a cure. Little is known about the effects of microgravity on the synovial joint and changes in cartilage homeostasis. Bone remodeling occurs much faster. This is the first study to use an in vitro and ex vivo approach to understand the effects of reduced gravity on cartilage health and to elucidate the signaling pathways responsive to changes in gravitational forces. Understanding changes in cartilage homeostasis and molecular pathways in reduced gravity conditions, will help us elucidate the mechanisms involved in disuse OA here on Earth, and develop novel therapeutic targets.
Task Progress:	This is the first study to show cartilage degradation at both the cell and tissue level in response to simulated microgravity via changes in gene expression, protein expression, and GAG (glycosaminoglycan) content. Although it appears that cartilage degradation in response to microgravity may take longer than bone density loss and skeletal muscle atrophy, cartilage tissue does not regenerate. Loss or degeneration of articular cartilage results in painful and debilitating joint disease that can limit mobility of the affected joint. We also targeted a potential signaling pathway that responds to mechanical unloading in chondrocytes. Active canonical Wnt signaling is essential in bone to maintain a balance between osteoclast and osteoblast activity. Inhibition of Wnt signaling has been correlated with bone loss. We detected inhibition of Wnt signaling in response to simulated microgravity in chondrocytes by up-regulation of sclerostin and other Wnt inhibitors. However, in cartilage, Wnt inhibition has been reported to be a chondro-protective mechanism to prevent further cartilage degradation, and canonical Wnt signaling has been associated with cartilage degradation and OA. We showed in our chondrocyte cell line that up-regulation of catabolic genes in response to simulated microgravity was similar to that of IL-1ß treatment. However, when recombinant sclerostin was added to IL-1ß treated cells, it decreased MMP (matrix metalloproteinase) expression as previously suggested, providing supportive evidence of the chondroprotective role of sclerostin in cartilage tissue. Therefore, it appears that sclerostin has opposite roles in these two adjacent tissues, and therapeutic targets using a sclerostin antibody to reduce bone density loss in space and osteoporosis need to be further evaluated given the potential of sclerostin inhibition resulting in the progression of OA. Funding for this project has helped provide new evidence for another tissue potentially affected by lack of gravity. Osteoarthritis and joint degradation may take longer than osteopenia or sarcopenia to develop, but unlike bone and muscle, cartilage degradation is irreversible and therefore, should be taken into consideration as a possible risk during prolonged spaceflight.
Bibliography Type:	Description: (Last Updated: 11/12/2020)
Articles in Peer-reviewed Journals	Mellor L, Mohiti-Asli M, Williams J, Kannan A, Dent MR, Guilak F, Loboa E. "Extracellular calcium modulates chondrogenic and osteogenic differentiation of human derived adipose stem cells: A novel approach for osteochondral tissue engineering using a single stem cell source." Tissue Eng Part A. 2015 Jun 2. [Epub ahead of print] PubMed PMID: 26035347 ; http://dx.doi.org/10.1089/ten.TEA.2014.0572 , Jun-2015

Articles in Peer-reviewed Journals	Mellor LF, Baker TL, Brown RJ, Catlin LW, Oxford JT. "Optimal 3D culture of primary articular chondrocytes for use in the rotating wall vessel bioreactor." Aviation, Space, and Environmental Medicine. 2014 Aug;85(8):798-804. PubMed PMID: 25199120; PubMed Central PMCID: PMC4207436 ; http://dx.doi.org/10.3357/ASEM.3905.2014 , Aug-2014
Articles in Peer-reviewed Journals	Mellor LF, Steward AJ, Nordberg RC, Taylor MA, Loboa EG. "Comparison of simulated microgravity and hydrostatic pressure for chondrogenesis of hASC." Aerosp Med Hum Perform. 2017 Apr;88(4):377-84. https://doi.org/10.3357/AMHP.4743.2017 ; PubMed PMID: 28518000 , Apr-2017
Articles in Peer-reviewed Journals	Mellor LF, Nordberg RC, Huebner P, Mohiti-Asli M, Taylor MA, Efird W, Oxford JT, Spang JT, Shirwaiker RA, Loboa EG. "Investigation of multiphasic 3D-bioplotted scaffolds for site-specific chondrogenic and osteogenic differentiation of human adipose-derived stem cells for osteochondral tissue engineering applications." J Biomed Mater Res B Appl Biomater. 2020 Jul;108(5):2017-30. Epub 2019 Dec 27. https://doi.org/10.1002/jbm.b.34542 ; PMID: 31880408; PMCID: PMC7217039 , Jul-2020
Articles in Peer-reviewed Journals	Nordberg RC, Mellor LF, Krause AR, Donahue HJ, Loboa EG. "LRP receptors in chondrocytes are modulated by simulated microgravity and cyclic hydrostatic pressure." PLoS One. 2019 Oct 4;14(10):e0223245. https://doi.org/10.1371/journal.pone.0223245 ; PMID: 31584963; PMCID: PMC6777824 , Oct-2019
Awards	Mellor LF. "Career advancement award, National Space Biomedical Research Institute, December 2014." Dec-2014
Awards	Mellor LF. "Fellow Travel Award, Biomedical Engineering Society (BMES)-CMBE annual meeting, January 2015." Jan-2015
Awards	Mellor LF. "Poster competition award, 3rd place Postdoctoral Research Symposium at NC State University, May 2014." May-2014
Awards	Mellor LF. "Professional Development Award, NCSU (NC State University) Postdoctoral Association, September 2014." Sep-2014