Fiscal Year:	FY 2019	**Task Last Updated:**	FY 06/11/2019
PI Name:	Lawler, John Ph.D.		
Project Title:	Upstream Regulation of Nox2 and Skeletal Muscle Atrophy During Microgravity and Countermeasure Development		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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:	77843	**Congressional District:**	17
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2016-17 Space Biology (ROSBio) NNH16ZTT001N-FG. App G: Flight and Ground Space Biology Research
Start Date:	06/01/2019	**End Date:**	07/31/2022
No. of Post Docs:		**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA ARC
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Flight Program:			
Flight Assignment:	NOTE: Start/end dates changes to 6/1/2019-7/31/2022 (originally 3/1/2019-5/31/2022) per NSSC award documents per F. Hernandez/ARC (Ed., 12/3/2020)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Fluckey, James Ph.D. (Texas A & M, College Station)		
Grant/Contract No.:	80NSSC19K0432		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Skeletal muscles are dynamic mechanical and metabolic machines that drive body movement and energy expenditure. Skeletal muscles are dynamic tissues that can adapt quickly to alterations in mechanical unloading by altering their mass and muscle fiber cross-sectional area. Skeletal muscle strength and endurance are essential to the health, well-being, and performance of astronauts during spaceflight and upon return to a gravitational environment. The mechanical unloading due to the microgravity (μG) of spaceflight causes muscle fiber atrophy and fiber-type shift of postural muscles in the lower extremities and flexors in the upper extremities. Microgravity also increases the risk of skeletal muscle damage, weakness, and thus the risk of injury upon reloading (e.g., extravehicular activities, Mars). Mechanotransduction is the ability to sense and regulate adaptive responses to increased or decreased loading. New paradigms have emerged from ground analogs of μG that have contributed to a leap of our understanding of mechanotransduction and muscle atrophy. Specifically, the mu-splice variant of neuronal nitric oxide synthase (nNOSμ) was discovered as causal in both muscle hypertrophy with overloading and atrophy with unloading. Our laboratory has found that reactive oxygen species (ROS) directly contribute to both muscle fiber atrophy and fiber-type shift from slow to fast. Pilot Data and cutting-edge research have identified mitochondria, the Nox2 isoform of NADPH oxidase, and upstream angiotensin II receptor 1 (AT1R) as sources of ROS during mechanical unloading. Preliminary Data show that inhibition of Nox2 translocation of nNOSμ away from the sarcolemma, muscle fiber atrophy, and fiber-type shift. However, the upstream mechanisms that regulate Nox2 during μG are poorly understood, impeding progress in space biology and novel countermeasure development. The lack of such knowledge impedes our development in understanding the mechanisms that underlie redox regulation of mechanotransduction in skeletal muscle. This grant application serves as a renewal and extension and Renewal of our research team's NNX13AE45G award, particularly stretching our horizons in understanding how Nox2 assembly is enhanced during microgravity in skeletal muscle. New studies have identified novel inhibitors for proteins recently govern assembly of the Nox2 complex at the cell membrane acid—sphingomyelinase (ASMase) and cyclophilin A. We hypothesize that the following novel countermeasures will protect against nNOSμ translocation and the spaceflight phenotype— (a) the ASMase inhibitor etidronate (Didronel) and (b) cyclophilin A inhibitor TMN-355. We further postulate that Nox2 is causal in ROS-induced suppression of anabolic signaling. The efficacy and specificity of the above countermeasures will be confirmed with gene knockdown experiments. Texas A&M is a rich research environment for NASA research, including the Space Life Science Program. We will use the latest molecular and image analysis tools in the development of highly novel countermeasures against spaceflight sarcopenia during microgravity. Dr. Lawler and Dr. Fluckey's laboratories have continued to be supported by NASA, and are dedicated to finding targeted, antioxidant countermeasures against spaceflight sarcopenia. The ground hindlimb unloading model will be used in short and long-term experiments. Our research will also directly translate to skeletal muscle wasting in clinical setting on Earth, an important mission of the Space Biology program. For example, hospitalization, particularly in an ICU (intensive care unit) can reduce skeletal muscle by 25%. Cast immobilization can decrease affected muscle mass by 30% as well. In addition, mechanical unloading due to disuse (e.g., bedrest) and illness (e.g., sepsis, chronic obstructive pulmonary disease, chronic heart failure) exacerbates atrophy, weakness, and impedes recovery.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research will also directly translate to skeletal muscle wasting in clinical setting on Earth, an important mission of the Space Biology program. For example, hospitalization, particularly in an ICU (intensive care unit) can reduce skeletal muscle by 25%. Cast immobilization can decrease affected muscle mass by 30% as well. In addition, mechanical unloading due to disuse (e.g., bedrest) and illness (e.g., sepsis, chronic obstructive pulmonary disease, chronic heart failure) exacerbates atrophy, weakness, and impedes recovery.
Task Progress:	New project for FY2019.
Bibliography Type:	Description: (Last Updated: 11/16/2023)