Fiscal Year:	FY 2007	**Task Last Updated:**	FY 02/01/2008
PI Name:	Reid, Michael B. Ph.D.		
Project Title:	Redox Modulation of Skeletal Muscle Function in Microgravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI Teams		
Program/Discipline--Element/Subdiscipline:	NSBRI Teams--Muscle Alterations and Atrophy Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Muscle**:Risk of Impaired Performance Due to Reduced Muscle Size, Strength and Endurance		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	40536-0298	**Congressional District:**	6
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2004 NSBRI NNH04ZUU003N Human Health in Space
Start Date:	09/01/2005	**End Date:**	08/31/2009
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Jones, Jeffrey (NASA JSC) Kennedy, Ann (University of Pennsylvania) Sabet, Arman (University of Kentucky)		
Grant/Contract No.:	NCC 9-58-MA00701		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	NASA's Critical Path Roadmap identifies loss of skeletal muscle function as a key concern for long-term missions. Gravitational unloading causes weakness of antigravity muscles due to loss of muscle mass (atrophy) and contractile dysfunction. In selected conditions, especially extravehicular activity (EVA), performance can also be limited by muscle fatigue. The current project evaluates selected compounds, nutritional supplements and pharmacologic agents, that may oppose oxidative stress in muscle and protect against weakness and fatigue. The experimental approach is designed to identify and develop countermeasures for human testing in the near-to-mid term. Initial experiments will define the loss of oxidant regulation that occurs with muscle unloading. Subsequent studies will evaluate compounds for protective effects on muscle function. The efficacy of each compound tested in this project is supported by preliminary data from animal studies, human trials, or both; each compound is approved for systemic administration to humans. Experiments will address three specific aims: Aim 1. To determine the time course, composition, and source of increased oxidant activity in unloaded muscle. Experiments will use mice conditioned by hindlimb unloading for up to two weeks. The antigravity muscle soleus will be studied to define the time course of oxidant dysregulation after unloading, to determine the relative contributions of reactive oxygen species vs. nitric oxide derivatives, and to test mitochondria as the primary source of increased oxidant activity. Aim 2. To evaluate selected antioxidants as countermeasures for weakness in unloaded muscle. In these experiments, mice conditioned by hindlimb unloading will be treated with one of four interventions that oppose oxidant activity or oxidant-mediated signaling: allopurinol (xanthine oxidase inhibitor), curcumin (NF-kappaB inhibitor), Bowman-Birk inhibitor complex (protease inhibitor), or N-acetylcysteine (NAC; reduced thiol donor). Unloaded soleus will be tested for protection against oxidative stress, contractile dysfunction, and muscle atrophy. Aim 3. To test NAC as a countermeasure for handgrip fatigue in humans. Experiments in healthy volunteers will define the appropriate preparation (solution vs. capsule) and dosage for oral NAC administration and will test NAC effects on handgrip strength and handgrip fatigue during concentric exercise.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research directly addresses two Earth-based problems, loss of function in unloaded muscle and muscle fatigue. The first problem occurs in individuals who are immobilized by injury or surgery. Muscles of the affected limbs atrophy and weaken, making it difficult for the individual to return to normal daily activity. The resulting inactivity lessens the quality of life, increases hospitalization and therapeutic costs, and increases the likelihood of pneumonia, venous thromboses, and other serious medical complications. A practical countermeasure to lessen atrophy and weakness would directly benefit these individuals, lessening the problems caused by transient immobilization. The second problem is familiar to us all. Acute muscle fatigue is a common feature of strenuous exercise. A countermeasure to inhibit fatigue would benefit a broad range of the US populace whose work requires physical exertion ranging from military professionals to firefighters, from police officers to construction workers. The implications for professional athletes are all too obvious.
Task Progress:	Our project is designed to address three sets of tasks, also known as specific aims. Our progress on each of these tasks over the previous year is summarized below: Task 1. Experiments originally proposed for Aim 1 are complete. We are extending this line of research by a new series of studies that test for changes in muscle and bone gene expression during gravitational unloading. DNA microarray techniques are being used to screen for genes that regulate muscle and bone growth, catabolism, and redox homeostasis. We seek novel markers of tissue adaptation and new targets for therapeutic intervention. Task 2. Our most recent study tested Bowman-Birk inhibitor complex (BBIC), a soybean-derived nutritional supplement, for effects on unloaded muscle. Soleus muscles of mice fed BBIC exhibited lower intracellular oxidant activity, less atrophy, and a smaller decrement in specific force. These data confirm previous findings by other investigators that BBIC protects unloaded muscle in mice and provide the first direct evidence that BBIC has antioxidant properties. In combination, the available data identify BBIC as an attractive compound for future tests in humans, i.e., during bedrest. Experiments proposed for original Aim 2 are now complete. To extend this work, we have begun collaborations with Unilever, a major international corporation in the field of food products and nutrition. We are working with scientists at Unilever to test novel nutritional interventions that may preserve muscle and bone during unloading. Task 3. Our progress on Aim 3 has been hampered by the unexpected departures of two key personnel. Our study coordinator and medical advisor each left Kentucky for positions outside the state. We have subsequently recruited outstanding replacements. Dr. Leonardo Ferreira, a postdoctoral fellow trained in redox biology and muscle metabolism, is the new study coordinator. Our new medical advisor is Dr. Leigh Ann Callahan, a board certified subspecialist in pulmonary and critical care medicine. Both individuals have completed human studies training and are approved by the IRB to participate in our protocol. Dr. Ferreira is fully trained in use of the ergometer system and data collection software. He is now recruiting and training subjects to participate in NAC studies. Despite these considerable delays, we retain our original goal of completing all three study arms during the final year of the project.
Bibliography Type:	Description: (Last Updated: 08/24/2020)
Articles in Peer-reviewed Journals	Arbogast S, Smith J, Matuszczak Y, Hardin BJ, Moylan JS, Smith JD, Ware J, Kennedy AR, Reid MB. "Bowman-Birk inhibitor concentrate prevents atrophy, weakness and oxidative stress in soleus muscle of hindlimb-unloaded mice." J Appl Physiol. 2007 Mar;102(3):956-64. PMID: 17110517 , Mar-2007
Articles in Peer-reviewed Journals	Reid MB. "Free radicals and muscle fatigue: of ROS, canaries, and the IOC." Free Radic Biol Med. Epub 2007 Mar 12. Review. PMID: 18191753 , Mar-2007
Articles in Peer-reviewed Journals	Farid M, Reid MB, Li Y-P, Gerken E, Durham WJ. "Effects of dietary curcumin or N-acetylcysteine on NF-kappaB activity and contractile performance in ambulatory and unloaded murine soleus." Nutr Metab (Lond). 2005 Aug 26;2:20. PMID: 16124875 , Aug-2005

Books/Book Chapters	Moylan JS, Durham WJ, Reid MB. "Muscle, oxidative stress, and aging." in "Oxidative stress, exercise, and aging." Ed. H.M. Alessio, A.E. Hagerman. London : Imperial College Press, 2006, p. 109-124., Mar-2006