Fiscal Year:	FY 2009	**Task Last Updated:**	FY 05/12/2010
PI Name:	Reid, Michael B. Ph.D.		
Project Title:	Redox Modulation of Skeletal Muscle Function in 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) **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:**	1
No. of PhD Candidates:	2	**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:			
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, re-phrased from specific aims. Our progress over the previous year is summarized below: Task 1. To determine the time course, composition, and source of increased oxidant activity in unloaded muscle. Experiments use mice conditioned by hindlimb unloading for up to three weeks. The antigravity muscle soleus was excised for functional and biochemical assays to assess changes in oxidant regulation. Experiments to address Task 1 are complete. Related studies of muscle gene expression during acute gravitational unloading were also completed this year. Homologous studies of gene expression in unloaded bone are in progress. Task 2. To test selected antioxidants as possible countermeasures for weakness of unloaded muscle. Mice conditioned by hindlimb unloading were treated with compounds that oppose oxidant-mediated signaling via four distinct mechanisms: allopurinol, curcumin, Bowman-Birk inhibitor complex, or N-acetylcysteine (NAC). Soleus muscle atrophy and contractile function were monitored to assess countermeasure efficacy. Experiments to address Task 2 are complete. Task 3. To evaluate NAC as a countermeasure for handgrip fatigue in humans. We previously showed that NAC inhibits human muscle fatigue. A final series of experiments in healthy volunteers have optimized the preparation and dosage of oral NAC administration for use in future countermeasure testing. A related study has identified the antioxidant OTC as a promising anti-fatigue agent and an alternative to NAC.
Bibliography Type:	Description: (Last Updated: 08/24/2020)
Articles in Peer-reviewed Journals	Ferreira LF, Gilliam LA, Reid MB. "L-2-Oxothiazolidine-4-carboxylate reverses glutathione oxidation and delays fatigue of skeletal muscle in vitro." J Appl Physiol. 2009 Jul;107(1):211-6. PMID: 19407260 , Jul-2009
Articles in Peer-reviewed Journals	Reid MB. "Reactive oxygen species as agents of fatigue." Med Sci Sports Exerc. 2016 Nov;48(11):2239-46. https://doi.org/10.1249/MSS.0000000000001006 ; PMID: 27285492 , Nov-2016