Fiscal Year:	FY 2019	**Task Last Updated:**	FY 01/25/2019
PI Name:	Rana, Brinda Ph.D.		
Project Title:	Identification of Functional Metabolomic Alterations During the Simulated Spaceflight Environment		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
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) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (3) **Muscle**:Risk of Impaired Performance Due to Reduced Muscle Size, Strength and Endurance (4) **Osteo**:Risk Of Early Onset Osteoporosis Due To Spaceflight (5) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	92093-5004	**Congressional District:**	49
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-MIXEDTOPICS. Appendix E: Behavioral Health & Human Health Countermeasures Topics
Start Date:	03/04/2016	**End Date:**	09/30/2019
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:	1	**Monitoring Center:**	NASA JSC
Contact Monitor:	Norsk, Peter	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date is now 9/30/2019 per NSSC information (Ed., 3/12/19) NOTE: End date is now 3/03/2019 per NSSC information (Ed., 6/20/18)		
Key Personnel Changes/Previous PI:	January 2019: Drs. Saito and Schilling are no longer working on the project. New CoInvestigators Tomas Vaisar and Andy Hoofnagle from the University of Washington, Seattle were brought into the team to conduct mass spectrometry based proteomics on urine samples. This is a new aim that we have added based on findings from the NASA Twins Study. Dr. Ziegler (UC San Diego) was brought into the team to assist with interpreting the metabolomics results in relation with space physiology. Dr. Darshi was formerly a post-doctoral fellow in Dr. Sharma's lab; she is now a new investigator and is leading the targeted metabolomics assays for the project.		

COI Name (Institution):	Sharma, Kumar M.D. (University of Texas, San Antonio) Patel, Hemal H Ph.D. (University of California, San Diego) Vaisar, Tomas Ph.D. (University of Washington) Hoofnagle, Andy M.D., Ph.D. (University of Washington) Ziegler, Michael Ph.D. (University of California, San Diego) Darshi, Manjula Ph.D. (University of Texas, San Antonio) Macias, Brandon Ph.D. (Wyle Cardiovascular) Lee, Stuart Ph.D. (Wyle Cardiovascular Lab) Smith, Scott Ph.D. (NASA Johnson Space Center) Stenger, Michael Ph.D. (NASA Johnson Space Center)
Grant/Contract No.:	NNX16AG03G
Performance Goal No.:	
Performance Goal Text:	
Task Description:	The overall goal of the proposed study is to identify serum and urine biomarkers that can be used to improve risk prediction for physiological manifestations due to bed rest beyond current clinical measures and known predictors. Bed rest is a well-accepted model of spaceflight (simulating microgravity) that allows for the study of a larger number of subjects than is available in spaceflight, and thus is well-suited for more rapid evaluation of countermeasures and identification of potential biomarkers associated with deconditioning and countermeasure efficacy. Our study will focus on three physiological manifestations that are prevalent in crew members on long duration spaceflight and are also observed in bed rest and are the target of countermeasures: (1) altered cardiovascular function and potential sub-clinical manifestations of cardiovascular disease; (2) bone loss and increased fracture risk; and (3) muscle atrophy and decreased muscle strength. To achieve this goal, we are applying two complementary metabolomics approaches, targeted and untargeted, to serum and urine which were collected longitudinally (2 pre-bed rest; 2 during bed rest; 1 post bed rest) from 29 study participants who underwent a 70-day head down tilt bed rest with or without participation in countermeasures (exercise, N=10; exercise plus testosterone supplement, N=9). Because a number of physiological outcomes of bed rest may be attributed to dysregulation of mitochondrial function (e.g., respiration) and mitochondrial related glycolosis, the targeted aims of our study will focus on mitochondrial related metabolic pathways. The strength of our current proposal is to use a combination of untargeted and targeted metabolomics approaches followed by a state-of-the-art metabolomic flux assay which will characterize the functional consequence of the metabolites on mitochondrial related cellular and physiological pathways involved in the homeostasis of metabolomic function.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Space Research Related Impact: This study has the potential to identify novel biomarkers in plasma and urine to detect the risk for and monitor the progression of physiological outcomes induced by the spaceflight environment. Research Impact on Earth: The study has potential to identify the sequence of metabolic events leading to disruption of metabolic pathways in individuals experiencing temporary bed rest (e.g., during pregnancy) or permanent bed rest (e.g., due to aging or disabilities). In the future, countermeasures can be developed to target these pathways. Assay Development: We are optimizing the application of a high throughput mitochondrial flux assay (Seahorse Assay) to detect circulating factors that can alter changes in mitochondrial function (glycolysis and respiration). This assay can then be applied to investigate environmental factors impacting bioenergetics of different tissue and cells for both Earth and Space related research.
Task Progress:	We have conducted mass spectrometry based untargeted metabolomics assays for primary metabolism on 24 hour pooled urine samples from 29 study participants undergoing a 70 day head down tilt bed rest study. These subjects are from three study arms: 11 bed rest CONTROL subjects, 10 subjects in the EXERCISE arm of the study, and 8 subjects from the COMBINED EXERCISE AND TESTOSTERONE arm. We chose 7 time points representing pre-, during, and post- bed rest (10 and 6 days before bed rest, days 28 and 69 of bed rest, and after bed rest days 0, 2, and 6). Preliminary data analysis has identified the disruption of multiple metabolic pathways during bed rest including pathways involved in the mitochondria, which supplies cellular energy to cells. In addition, as expected the lactic acid increased after bed rest. We are in the process of conducting statistical analysis to assess the relationship between metabolic changes and the treatment of exercise and testosterone. We are also in the process of conducting targeted mass spectrometry based metabolomics assays, including a panel of targeted mitochondrial pathway metabolites. These metabolomics studies are being complemented by a study designed to measure whether changes in the milieu of factors circulating in the blood as a result of the simulated space environment and countermeasures may affect cellular metabolism. Using the Seahorse Technology (Agilent) we are determining the impact of plasma on mitochondrial respiration on an established skeletal muscle cell line. By examining the trajectory of mitochondrial respiration of L6 cells treated with plasma obtained from bed rest study participants at pre, during, and post time points, we can understand how the body adapts to physical inactivity (on Earth) or microgravity conditions in space.
Bibliography Type:	Description: (Last Updated: 07/30/2019)