Fiscal Year:	FY 2024	**Task Last Updated:**	FY 05/16/2024
PI Name:	Beheshti, Afshin Ph.D.		
Project Title:	Spaceflight and Regolith Induced Mitochondrial Stress Mitigated by miRNA-based Countermeasures		
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) Animal Biology: Vertebrate		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	(1) Translational (Countermeasure) Potential		
PI Email:	afshin.beheshti@nasa.gov	**Fax:**	FY
PI Organization Type:	NASA CENTER	**Phone:**	617-308-2540
Organization Name:	KBR/NASA Ames Research Center		
PI Address 1:	Space Biosciences Research Branch		
PI Address 2:	Mail stop N211-31		
PI Web Page:			
City:	Moffet Field	**State:**	CA
Zip Code:	94035	**Congressional District:**	16
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2022 Space Biology NNH22ZDA001N-SBR: E.9 Space Biology Research Studies
Start Date:	05/01/2024	**End Date:**	04/30/2026
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
Contact Monitor:	Griko, Yuri	**Contact Phone:**	650-604-0519
Contact Email:	Yuri.V.Griko@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Schisler, Jonathan Ph.D. (University of North Carolina) Schwartz, Robert M.D., Ph.D. (Weill Medical College of Cornell University) Mason, Christopher Ph.D. (Weill Medical College of Cornell University)		
Grant/Contract No.:	Internal Grant		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	It has been established that the space environment leads to accelerated aging, leading to immune dysfunction and liver problems, with a profound impact on mitochondrial function across many systems. The impact that the space environment has on the liver is of great concern during long-term space missions for astronauts; and currently, there exists a gap in knowledge on the key pathways and factors that are responsible for the associated health risks. In addition, even less is known of the impact of regolith on health in space. We believe that there is a critical circulating microRNA (miRNA) signature in the blood associated with mitochondrial dysfunction caused by the space environment that can be manipulated to alter metabolism to mitigate damage and improve human health in space. We have previously shown that mitochondrial dysfunction has a systemic impact on the body due to spaceflight and separately have shown that a miRNA spaceflight signature can drive universal health risks. In addition, we also have shown that the metabolic changes occurring in the liver can lead to lipid accumulation and have a direct impact on the immune system. This liver associated phenotype from the space environment is potentially very similar to a chronic disease in the clinic called Myalgic Encephalomyelitis/ Chronic fatigue syndrome (ME/CFS) with no current effective treatment options. Current research into ME/CFS is suggesting dysregulated energetics, issues with the immune system, and a dysbiotic gut could play a key role. In ME/CFS, there is an enhanced movement of bacteria from the gut into the bloodstream, resulting in increased microbial associated peptides. Astronauts show large changes in the gut microbiome in space, which is slow to normalize when they return to Earth. The additional exposure to regolith can potentially increase this change. Once pathogens enter the body via the gut, the next destination is the liver, and a sustained gut leak as a consequence of gut dysbiosis is likely to impact liver function over time. Mitochondria are now known to have a significant role in innate immunity, the first line of defense against pathogens. Mitochondrial stress as a consequence of space factors, or an influx of pathogens into the liver from a dysbiotic gut, will impact liver function and result in a mitochondrial response. Here, we hypothesize during spaceflight and regolith exposure the increase in oxidative phosphorylation (OXPHOS) in the liver is due to increases in mitochondrial DNA (mtDNA) driven by microRNAs (miRNAs) creating systemic impact on the body. By inhibiting these key miRNAs associated with changes in the body during spaceflight, we will be able to mitigate the damage caused to the liver and improve immune and mitochondrial functions. In addition, we have shown that inhibition of these miRNAs can lead to rescue of inflammatory, immune, and OXPHOS functions and improved efficiency with DNA double strand break (DSB) repair. To show the relationship of the impact this will have in the liver and link to the pathogen increase in the gut, we will use archived liver tissue for a baseline without regolith exposure from our previous experiments, which will include: 1) young and old mice from the Rodent Research Reference Mission-1 (RRRM-1) and Rodent Research Reference Mission-2 (RRRM-2) International Space Station (ISS) missions; and 2) mice irradiated with 0.5Gy galactic cosmic radiation (GCR) simulated beam with and without simulated microgravity, and with and without miRNA-based countermeasures. In addition, we will correlate omics data from the liver tissues available on NASA's Open Science Data Repository and astronaut data from Japan Aerospace Exploration Agency (JAXA) missions, the NASA Twins Study, and commercial spaceflight missions (i.e., Inspiration4 and Polaris Dawn). We will then utilize 3D human liver and microvasculature tissues exposed to regolith and GCR radiation to determine the additional molecular changes occurring. Lastly, we will test potential countermeasures in the 3D human tissues determined through established machine learning techniques to target the key miRNAs.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This data will allow, for the first time, determination of key systemic mitochondrial changes through circulating miRNAs that are impacted by the space environment and regolith exposure. In addition, this research will generate novel and crucial datasets with a metabolic focus. We believe, as with our previous work, we will be able to successfully complete this proposal, which will produce a novel method to: 1) monitor metabolic changes that occur during spaceflight/regolith exposure, and 2) manipulate the metabolism by using antagomirs specifically targeting mitochondrial functions.
Task Progress:	New Project for FY2024
Bibliography Type:	Description: (Last Updated: 07/10/2024)