Fiscal Year:	FY 2022	**Task Last Updated:**	FY 04/13/2022
PI Name:	Huang, Alex M.D., Ph.D.		
Project Title:	Exercise Countermeasure to Prevent Ocular Structural and Functional Changes in a Terrestrial Model of SANS		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **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:	92093-0946	**Congressional District:**	52
Comments:	The PI moved from Doheny Eye Institute to University of California, San Diego in 2023.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2018-2019 HERO 80JSC018N0001-SANS: Spaceflight Associated Neuro-ocular Syndrome Countermeasures. Appendix C
Start Date:	07/01/2020	**End Date:**	06/30/2023
No. of Post Docs:	0	**No. of PhD Degrees:**	7
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	8
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Stenger, Michael	**Contact Phone:**	281-483-1311
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	Ed. Note: Millennia Young, Ph.D., at NASA Johnson Space Center, was added to the project during this reporting period (per information from the Principal Investigator, 4/21/22).		
COI Name (Institution):	Laurie, Steven Ph.D. (KBR./NASA Johnson Space Center) Lee, Stuart Ph.D. (KBR/NASA Johnson Space Center) Macias, Brandon Ph.D. (NASA Johnson Space Center) Marshall-Goebel, Karina Ph.D. (KBR/NASA Johnson Space Center) Sadda, Srinivas M.D. (Doheny Eye Institute) Loerch, Linda M.S. (NASA Johnson Space Center) Young, Millennia Ph.D. (NASA Johnson Space Center)		
Grant/Contract No.:	80NSSC20K1034		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Optic disc edema develops in about 16% of astronauts during long-duration spaceflight and is of high concern to the NASA medical community and a target of therapeutic treatment given risk of vision loss. Currently, there is not a reliable method to predict which crewmembers will develop disc edema. Moreover, it was previously believed that only the spaceflight environment could produce optic disc edema in normal healthy subjects. Recently our research team developed a novel ground-based spaceflight analog that reproduced disc edema in healthy test subjects that can be used to test novel pathophysiological hypotheses and possible Spaceflight Associated Neuro-ocular Syndrome (SANS) countermeasures. The research outlined in this proposal will use this new ground-based spaceflight analog advanced by NASA to elucidate the structural and functional impact of optic disc edema and to evaluate alterations to retinal and optic nerve blood flow to understand their contributions to the etiology of SANS. Further, a novel countermeasure will be tested to prevent the development of disc edema, functional decline in ganglion cell function, and vascular alterations associated with this ground-based spaceflight analog. This proposal will (1) determine combined structural and functional ocular alterations caused by the development of optic disc edema in this spaceflight analog, (2) determine the role of altered vascular blood flow in the development of optic disc edema in this spaceflight analog, and (3) determine if daily aerobic exercise in combination with veno-occlusive thigh cuffs can be used as a preventative countermeasure against the formation of optic disc edema. Thus, this proposal utilizes a newly developed spaceflight analog and will allow us to test novel hypotheses for predicting, characterizing, and preventing the development of optic disc edema.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Outcomes of this research can benefit humans in space and on Earth. First, SANS is a hurdle to long-haul space travel. The ocular alterations in SANS can impact vision, which represents a major safety concern during spaceflight. Thus, better understanding SANS and developing countermeasures to mitigate SANS improves the safety of space travel. Then, the major pathophysiological hypothesis for why SANS is occurring is the idea of fluid shifts. This concept states that gravity normally pulls total body fluid to the lower extremities of humans, and without gravity this fluid re-distributes to the head. It is hypothesized that the increased volume in the head leads to SANS. Increased volume in the head can also lead to other clinical manifestations such as a sensation of facial fullness and increased intraocular (eye) or intracranial (brain) pressure. The latter are important in many Earth-bound diseases. For example, in glaucoma, head-ward fluid shifts are known to increase eye pressure which can lead to blindness. Thus, better understanding fluid shifts and how to minimize them may lead to additional benefit in the treatment of Earth-bound diseases.
Task Progress:	Ed. Note (6/15/23): This grant number has closed due to the PI's move to the University of California San Diego. A new project under Dr. Huang continues the work of "Exercise Countermeasure to Prevent Ocular Structural and Functional Changes in a Terrestrial Model of SANS. See Grant #80NSSC22K1803 for updated information. This study occurs in collaboration with the :envihab facility in the German Aerospace Center (DLR). Four campaigns are now associated with this study. The Aims, Methods, and Results of the second year of this proposal are described below: SPECIFIC AIMS Specific Aim 1: To determine if donning veno-occlusive thigh cuffs during and for 120 minutes after daily aerobic exercise can be used to (a) reverse headward fluid shift from bed rest for a sustained period of time, and (b) prevent ocular structural and functional changes from developing at the end of bed rest. Hypothesis 1a: Donning veno-occlusive thigh cuffs during and after daily aerobic exercise will provide an acute and sustained fluid redistribution into the lower extremities (measured using femoral artery conductance and vasculature cross-sectional area) with a corresponding reduction in internal jugular vein cross-sectional area for up to 2 hours after cessation of exercise. Hypothesis 1b: There will be a decrease in prevalence and magnitude of optic disc edema in subjects performing the exercise countermeasure (CM) outlined in Specific Aim 1 (SA1) compared to subjects in the head-down tilt group who perform no CM. Advanced analyses of optical coherence tomography (OCT) images of the optic nerve head, combined with electrophysiological assessment of ganglion cell function, will unveil functional decline and together may serve as a more sensitive endpoint compared to the visual fields tests currently used in astronauts. Specific Aim 2: To determine the role of altered vasculature in the development of optic disc edema in this spaceflight analog. [Ed. Note: This spaceflight analog is the :envihab facility at the Deutsches Zentrum für Luft- und Raumfahrt (DLR) in Cologne, Germany.] Hypothesis 2a: Optical coherence tomography angiography (OCTA) will reveal vascular alterations in the foveal avascular zone (FAZ) area or vascular density in the macula and nerve with intravenous fluorescein angiography showing leakage in subjects demonstrating the greatest degree of retinal thickening. Hypothesis 2b: There will be a decrease in OCTA and intravenous fluorescein angiography alterations in subjects performing exercise CM outlined in SA1 compared to subjects in the head-down tilt group who perform no CM. MATERIALS AND METHODS This study is scheduled to occur at the :envihab facility in the German Aerospace Center (DLR). Previously, six campaigns were associated with this study. The six arms of the study included (1) an upright control, and (2) a 60-day bed rest 6-degrees head-down tilt (HDT) control. All experimental arms included the 30-day 6-degrees bed rest HDT condition combined with four CMs: (1) veno-occlusive thigh cuffs and exercise, (2) lower-body negative pressure (LBNP), (3) a B-vitamin supplement, and (4) a 6-hour upright posture CM. The CM focus of this proposal is #1. During this last year, and due to research resources re-focusing during the COVID-19 pandemic, two arms were removed from this study, the upright control and CM #3. For this proposal, the exercise and veno-occlusive thigh cuff CM will be performed 6 days a week. Each session will include exercise (60 min) that will be sustained at ~60% of pre-bedrest peak oxygen consumption with the veno-occlusive thigh cuff applied at 60 mm Hg for two hours after exercise cessation. Endpoints will be measured before, during, and after the study. These include intraocular pressure (IOP), optical coherence tomography (SPECTRALIS HRA+OCT imaging platform) of the macula and optic nerve, ultrasound measure of neck and lower extremity vessels, optical coherence tomography angiography (OCTA) of the macula and optic nerve, and electrophysiology for ganglion cell function. Intravenous fluorescein angiography (IVFA) will be performed to assess blood:brain vascular integrity at the optic nerve head immediately after cessation of the 30-day bed rest period.

	Overall, OCTA, IVFA, and electroretinogram (ERG) endpoints will be assessed across all arms in addition to subjects in the CM #1 group. RESULTS This study is scheduled to occur at the :envihab facility at the German Aerospace Center (DLR). There are 4 campaigns. Campaigns 1 and 2 (C1/C2) were scheduled to be comprised of 12 subjects each. For each group of 12, 6 subjects received the upright CM, and 6 subjects received the LBNP CM. C1 ended in December 2021 (12/2021) with data acquired from 12 subjects. C2 just finished in March 2022 (3/2022) with data acquired from 11 subjects (5 upright CM and 6 LBNP CM). One subject (with the upright CM) from C2 was removed from the study due to failure to follow instructions. Data analysis is now underway for the C1 and C2 OCTA, ERG, and IVFA results. Campaigns 3 and 4 (C3/C4) are comprised of 12 subjects each and involve the cuff and exercise CM and HDT control subjects. C3 and C4 are scheduled to begin in the end of 2022, with all data acquired projected in mid-2023.
Bibliography Type:	Description: (Last Updated: 06/07/2023)