Fiscal Year:	FY 2020	**Task Last Updated:**	FY 12/08/2020
PI Name:	Zwart, Sara Ph.D.		
Project Title:	B Complex: 5-Methyltetrahydrofolate, Riboflavin, Pyridoxine, and Methylcobalamin Supplementation as a Non-Mechanical Countermeasure to Mitigate Optic Disc Edema Changes During Strict 6° Head-Down Tilt Bed Rest		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
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Human Research Program Risks:	(1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
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Space Biology Special Category:	None		
PI Email:	sara.zwart-1@nasa.gov	**Fax:**	FY
PI Organization Type:	NASA CENTER	**Phone:**	281-483-3753
Organization Name:	NASA Johnson Space Center		
PI Address 1:	Department of Preventive Medicine and Community Health		
PI Address 2:	2101 Nasa Pkwy, Mail Stop SK3		
PI Web Page:			
City:	Houston	**State:**	TX
Zip Code:	77058-3607	**Congressional District:**	36
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COI Name (Institution):	Chen, John M.D., Ph.D. (Mayo Clinic Rochester) Egert, Sarah Ph.D. (University of Hohenheim, Germany) Heer, Martina Ph.D. (Rheinische Friedrich-Wilhelms-Universitat Bonn, Germany) Laurie, Steven Ph.D. (KBR/NASA Johnson Space Center) Macias, Brandon Ph.D. (KBR/NASA Johnson Space Center) Smith, Scott Ph.D. (NASA Johnson Space Center)		
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Task Description:	Approximately 20% of astronauts on International Space Station (ISS) missions have experienced ophthalmic pathologies including optic disc edema, one aspect of what is characterized as Spaceflight Associated Neuro-ocular Syndrome, or SANS. While the precise cause for SANS is not known, it is likely that there are multiple contributing factors, including genetic and environmental factors that may affect the response to headward fluid shifts. B-vitamin status, one carbon biochemistry, and the presence of specific one-carbon metabolic pathway single nucleotide polymorphism (SNP) alleles were significant predictors for the incidence of astronaut ophthalmic pathologies, including optic disc edema, choroidal folds, and cotton wool spots. When looking at the individual SNPs, the G allele of methionine synthase reductase (MTRR, rs1801394) A66G and the C allele of serine hydroxymethyltransferase-1 (SHMT1, rs1979227) C1420T were associated with higher incidence of spaceflight-induced ophthalmic changes compared to those with the A or T alleles. In ground-analog studies, end-tidal CO2, a reflection of arterial CO2, response to acute head-down tilt (HDT) and CO2 exposure was also related to G and C alleles of MTRR A66G and SHMT1 C1420T and B-vitamin status. Likewise, in a recent bed rest study where subjects were exposed to strict 6°-HDT bed rest and 0.5% CO2 for 30 days, 5 out of 11 subjects developed optic disc edema. The number of SHMT1 C1420T C and MTRR A66G G alleles were significantly associated with the change in total retina thickness, a quantitative measure of optic disc edema. There are several possibilities to explain how one-carbon metabolism could lead to the ocular phenotypes in some individuals after spaceflight or bed rest. One-carbon metabolism is intimately involved in maintaining endothelial function through maintenance of endothelial nitric oxide (NO) synthase and NO production. We have proposed a multi-hit hypothesis, with genetics and B vitamin status, along with potential factors or “multiple hits” contributing to endothelial dysfunction (e.g., CO2 exposure, fluid shifts, altered endocrine function, radiation exposure). The resulting endothelial dysfunction could lead to cerebral microvascular edema, which can impede cerebrospinal fluid outflow and impinge on the optic nerve and eye. Furthermore, decreased NO and increased peroxynitrite can also affect collagen and elastin integrity through activation of matrix metalloproteinases (MMPs). Specifically, MMP activation can affect collagen and elastin cross-linking, firmness, and elasticity, particularly in the sclera and lamina cribrosa, which are collagen-containing layers of the eye. Differences in elasticity of the sclera and lamina cribrosa could affect an individual’s response to a headward fluid shift during bed rest or spaceflight. Dietary B-vitamin insufficiencies and variants in genes involved in the one-carbon metabolic pathway can contribute to pathway inefficiency, which can affect numerous outcomes, including NO production and endothelial function. This would also explain why after exposure to microgravity, fluid shift, CO2, and/or other factors – only a subset of individuals develop optic disc edema. We hypothesize here that supplementing with required cofactors (i.e., B-vitamins) can increase one-carbon pathway efficiency and ultimately prevent or mitigate spaceflight- and bed rest-induced optic disc edema.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	New project for FY2020.
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