Fiscal Year:	FY 2022	**Task Last Updated:**	FY 07/27/2021
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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		
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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)		
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Space Biology Special Category:	None		
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Zip Code:	77058-3607	**Congressional District:**	36
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Key Personnel Changes/Previous PI:	No changes		
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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:	The implications of this research for one of NASA’s highest priority crew health risks are significant, along with the implications for a better understanding of the role of one-carbon metabolism in the health of the general population.
Task Progress:	After receiving Authority to Proceed on August 30, 2019, Institutional Review Board (IRB) documentation was developed and submitted for review. IRB approval was obtained in May 2020 and a renewal was approved in April 2021. The SANS Countermeasures selected for this study have been reduced to 4 campaigns (from 6 originally planned) due to the regulatory burden at DLR (German Aerospace Center) that would be required to support this B-Complex study. The study would have been classified as a Clinical Trial, and DLR was not poised to support such a study. The current timeline for the 4 campaigns is Campaign 1 and 2 – lower body negative pressure (LBNP) and 6-hour seated (12 subjects per campaign) – Campaign 1 baseline data collection (BDC) start 09/28/2021, Campaign 2 BDC start 01/24/2022; Campaign 3 and 4 – exercise CM (countermeasure) and strict head down tilt (HDT) (12 subjects per campaign) – Campaign 3 and 4 BDC start TBC but likely during 2023. Despite the fact that the B-Complex supplement will not be tested in this study, all of the genetics and biochemistry analyses from our proposed study are still planned for the 4 campaigns. An Investigator’s Working Group meeting is scheduled for September 1, 2021.
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