Fiscal Year:	FY 2024	**Task Last Updated:**	FY 03/11/2024
PI Name:	Gonzalez-Juarbe, Norberto		
Project Title:	Understanding the Impact of Hypobaric Hypoxia and Confinement Stress on Intestinal Immunity and Host-Microbiome Interactions		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H)		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **Hypoxia**:Risk of Reduced Crew Health and Performance Due to Hypoxia [inactive]		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	20850-6380	**Congressional District:**	6
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2019 HERO 80JSC018N0001-HHCHFBP: Human Health Countermeasures, Human Factors, Behavioral Performance. Appendix D
Start Date:	05/10/2021	**End Date:**	12/10/2023
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:		**No. of Master' Degrees:**	1
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Whitmire, Alexandra	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/10/2023 per NSSC information (Ed., 7/6/23). NOTE: End date changed to 05/10/2023 per NSSC information (Ed., 6/6/22).		
Key Personnel Changes/Previous PI:	Original PI: Dr. Hernan Lorenzi, Co-investigators: Dr. Norberto Gonzalez-Juarbe and Dr. Yanbao Yu. After Dr. Lorenzi's departure, Dr. Manolito Torralba took over the project, however he also left the institute during the pandemic. Dr. Norberto Gonzalez-Juarbe took over the project after Dr. Torralba left. The COVID-19 pandemic delayed the start of the project and in addition caused multiple personnel changes at the institute. Note: Per the PI, Dr. Alexander Chouker of Ludwig-Maximilians-University has continued as a Collaborator with this investigation (Ed., 4/4/24).		
COI Name (Institution):			
Grant/Contract No.:	80NSSC21K1116		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

Background:
It is expected that future crewed space missions involving extravehicular activities (EVA) will require novel EVA architectures including a slightly hypobaric hypoxic cabin atmosphere (8.2 psia, 34% O2). Humans are well-adapted to live at Earth altitudes with similar O2 partial pressures. However, it is not clear if the combined effect of hypobaric hypoxia (HH) with other space-associated stressors such as microgravity, altered circadian rhythm or confinement, will have a synergistic detrimental effect on crew health. Several studies suggest that some hypoxic conditions may affect the host immune response and gut microbiota (1-4). Also, healthy individuals exposed for ~1-year to the HH environment of the Antarctic Concordia station show immune sensitization (5, and Life Sciences Data Archive (LSDA) experiment: Confinement and Hypobaric Hypoxia on Immunity in the Antarctic Concordia Environment (CHOICE)). The Antarctic Neumayer and Concordia stations represent a high-fidelity spaceflight ground analog, reflecting some conditions of long-duration space missions, such as extreme isolation and altered circadian rhythm. Neumayer is a coastal base located at the sea level. Concordia resides 1,000 km inland at an altitude of 3,232 m and therefore, has a HH environment. Herein, we propose to investigate the combined impact of long-term HH and isolation on the human microbiome and immune system homeostasis in the intestinal tract by using an existing collection of stool specimens derived from 34 healthy individuals that spent ~1-year at either the Concordia or Neumayer stations.

Hypothesis:

We hypothesize that the combined effect of HH and confined environment stressors will induce changes to the human intestinal immune response and gut microbiota in the context of microbial diversity, activity, composition, and protein post-translational modifications (PTMs, such as acetylation and oxidation), which tend to be associated with impaired host metabolism, immune response and aggravated cellular damage (1, 2).

Aims:

Aim 1, we will look at the effect of long-term exposure to HH in conjunction with extreme confinement on the human microbiome and intestinal immune response. We will use molecular markers to characterize changes in the microbial composition of the human gut microbiome. Changes in the gut microbiota have been found associated with chronic inflammatory diseases such as Inflammatory Bowel Disease, metabolic disorders, and increased permeability of the gut epithelium. Complementing these studies, we will also perform global metaproteomics of the protein fraction of human stool samples. These analyses will shed light into the effect of HH and confinement on intestinal immune response, gut microbiota metabolism and gut epithelium integrity.

Aim 2, we will investigate the effect of long-term exposure to hypobaric hypoxia and confinement on acetylation and oxidation status of microbial and host proteins in the human gut. Protein acetylation is involved in epigenetic regulation of gene expression and in modulation of enzymatic activity and protein-protein interactions. Therefore, our proposed studies will inform about alterations in metabolic activity of the gut microbiome and, potentially, of the gut epithelium. In addition, proteomic analysis of the oxidation state of microbial and host proteins in the gut will allow us to assess the impact of HH and confinement on oxidative stress and damage in the human gut and microbiome. To our best knowledge, there is very little information about how the combination of HH and confinement stressors affect the human microbiome composition and metabolic activity and the intestinal immune response. Therefore, the product of this study will be information that will help to define the likelihood and consequences of the risk of reduced crew health due to long-term HH exposure and will dramatically decrease the degree of uncertainty in this risk.

Methods:

Stool specimens were collected from healthy individuals before, during, and after a ~1-year stay at the Neumayer or Concordia stations and kept frozen for further analysis at the J. Craig Venter Institute. We will apply the well-established protocols in our laboratories to extract genomic DNA and proteins from stool samples for taxonomic profiling and proteomic analyses.

Deliverables:

A detailed qualitative and quantitative analysis of the impact of Neumayer and Concordia extreme conditions and HH on human gut microbiome and host immunity, interpretation of identified microbial PTMs, and assessment of potential risks to human health.

Significance:

The crosstalk between the intestinal microbiome and immune system is essential to human health. Understanding the response of intestinal microbiota and immunity to extreme stress conditions at the taxonomic, metaproteome and PTM levels will offer novel insights into the immune system-microbiome interactions during HH and isolation conditions, and may set the bases for potential therapeutic targets for spaceflight-induced immune and microbial dysregulation.

References:

1. Zhang X, Ning Z, Mayne J, Deeke SA, Walker K, Farnsworth CL, Stokes MP, Mack D, Stintzi A, Figeys D. Deep characterization of the protein lysine acetylation in human gut microbiome and its alterations in patients with Crohn's disease. Systems Biology. bioRxiv; 2019. p. 337

2. Berlett BS, Stadtman ER. Protein oxidation in aging, disease, and oxidative stress. J Biol Chem. 1997 Aug 15;272(33):20313–20316. PMID: 9252331

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:	Our studies inform about alterations in metabolic activity of the gut microbiome and, potentially, of the gut epithelium due to confinement and hypoxia leads to modulation of inflammation. In addition, proteomic analysis of microbial and host proteins in the gut will allow us to assess the impact of HH and confinement on host-microbiome interactions and how they correlate to inflammatory profiles. To our best knowledge, there is very little information about how the combination of HH and confinement stressors affect the human microbiome composition and metabolic activity and the intestinal immune response. Therefore, the product of this study is information that will help to define the likelihood and consequences of the risk of reduced crew health due to long-term HH exposure and will dramatically decrease the degree of uncertainty in this risk.
Task Progress:	Task-1: Processing of stool samples and generation of 16S taxonomic profiles: Our group has extracted DNA from 428 samples that cover the effects of long-term hypobaric hypoxia (HH) and confinement on the human gut microbiome from stool samples that were collected from subjects spending one year in confinement in Antarctica at either the coastal base Neumayer or at the high-altitude Concordia base. Task-2: Analysis of 16S taxonomic profiles and stressors associated to the Concordia and Neumayer stations. Current analysis of the 16S data shows that the microbial composition of the crew members of Concordia and Neumayer is altered depending on the time of the year and is different when comparing each station against each other. Task-3: Extraction of stool proteins and global metaproteomics analysis. Our group has processed over 100 pooled samples for global proteomic analysis. All samples are in the queue at the mass spec facility. Task-4: Integration of proteomics, 16S and inflammation data. We were able to compare data on circulating inflammation markers (cytokines and chemokines) with gut microbial changes and gut proteomic changes. This analysis showed a strong correlation of proteins associated with inflammation, cardiac and liver dysfunction, changes in metabolism, and insulin resistance with specific gut bacterial changes. Overall, this study has discovered how proteomics and microbiome analyses can be used to define novel biomarkers for changes induced by hypoxia and confinement in cardiac health, metabolic changes, circulating inflammation, and overall gut health. Microbial analysis showed that gram-negative bacteria and other pathogenesis-associated bacteria increase throughout the year in both Neumayer and Concordia, with beneficial bacteria being reduced. Concordia showed more pronounced bacterial changes when compared to Neumayer. The proteomic assessment showed increased gut proteins that are associated with cardiac muscle and liver dysfunction, promotion of insulin resistance, and gut epithelial changes that are associated with cancer development. Of note, a specific protein Galectin-4 (LEG4), shown to reduce inflammation in the gut in models of colitis was upregulated throughout the year after arrival at each base. Taken together, this study shows that stool may serve as a powerful human sample to assess the overall health of crewmembers in space analogs and in space.
Bibliography Type:	Description: (Last Updated:)