Fiscal Year:	FY 2020	**Task Last Updated:**	FY 06/29/2020
PI Name:	Rithidech, Kanokporn Ph.D.		
Project Title:	Effects of Space Flights on the Proteome of Astronauts' Plasma		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Immune**:Risk of In Mission Impacts, Adverse Health Events or Long-Term Health Impacts due to Altered Immune Response		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	11794-8691	**Congressional District:**	1
Comments:			
Project Type:	Flight	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-MIXEDTOPICS. Appendix E: Behavioral Health & Human Health Countermeasures Topics
Start Date:	04/01/2016	**End Date:**	12/31/2021
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Norsk, Peter	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	Flight definition NOTE: End date changed to 12/31/2021 per NSSC information (Ed., 12/31/20) NOTE: End date changed to 12/31/2020 per NSSC information (Ed., 6/12/20) NOTE: End date changed to 3/31/2020 per NSSC information (Ed., 3/25/19)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Martin, Dwight Ph.D. (State University of New York, Stony Brook)		

Grant/Contract No.:	NNX16AH80G
Performance Goal No.:	
Performance Goal Text:	
Task Description:	NOTE: This is an integrated project consisting of Dr. Brian Crucian's "Functional Immune Alterations, Latent Herpesvirus Reactivation, Physiological Stress, and Clinical Incidence Onboard the International Space Station" directed research; and Dr. Richard Simpson's "The Impact of an ISS Mission on the Anti-Viral and Functional Properties of NK-cells, T-cells, B-cells and Dendritic Cells," Dr. Kanokporn Rithidech's "Effects of Space Flights on the Proteome of Astronauts' Plasma," and Dr. Honglu Wu's "DNA Damage in the ISS Astronaut's Lymphocytes and Their Association with Stress-Induced Immune Dysfunction" solicited research. Space flight results in exposure of astronauts to several stressors, such as space radiation, microgravity, and physiological stress, that could exacerbate the risks of adverse health effects. To protect astronauts, we must improve our understanding of molecular changes that influence immunological conditions associated with increased astronaut health risks. The in vivo response to the space environment is complex, involving multiple proteins associated with various signal transduction cascades, resulting in different outcomes. Molecular mechanisms responsible for such diverse consequences are poorly understood. It is, therefore, essential to characterize the protein signatures of responses to the space environment in blood plasma samples from astronauts, collected at pre-, in-, and post-flights. Such analyses should help to reveal a particular set of proteins causing adverse immunological changes and to develop methods that help to prevent, or at least to counteract, these effects. In this flight definition project, we will use cutting age proteomic technology to determine protein alterations, qualitatively and quantitatively, in plasma samples collected from astronauts before, during, and after space flights. Our findings will help to provide an understanding of the time course and etiology of immune changes induced by the space environment. Furthermore, since pre- and post-flight samples, in addition to the in-flight samples, will be evaluated in the same astronaut, the direct effects of the space environment can be determined. Hence, our findings will provide high-priority and highly relevant information to NASA. We will further correlate protein expression profiles to the available data on immune dysfunction detected in each astronaut. This approach makes it possible to determine potential predictive biomarkers for space-flight-induced immune dysregulation. Consequently, effective countermeasures against such harmful effects of the space environment can be identified.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our findings will deliver important information that should advance our understanding of the time course and etiology of immune changes induced by the space environment. Hence, our findings will provide high-priority and highly relevant information to NASA. Importantly, we will correlate protein expression profiles to the available data on immune dysfunction detected in each astronaut. This approach makes it possible to determine potential predictive biomarkers for space-flight-induced immune dysregulation. Such knowledge is important for assessment of health risks and will facilitate the development of appropriate countermeasures that can help astronauts, space travelers, and people on Earth with the impairment of the immune system.
Task Progress:	The major goal of our Flight Definition is to identify and characterize plasma proteins in the blood plasma of astronauts that can be used as predictive biomarkers of immunological dysfunction due to space flight. Specifically, we characterize the proteome of blood plasma collected from the same astronauts at different times, i.e., pre-, in-, and post-flight. In the last annual report, we reported that a total of 453 unique and non-redundant proteins were identified at >99% confidence. Changes in protein concentrations during the pre-, in-, and post-flight timeline were determined by Students' t-test analysis of comparisons between groups ($p<0.1$ is considered significant). Our data demonstrate that there are 14 proteins with significant changes, i.e., increased or decreased, in expression levels in plasma samples collected in-flight as compared to those collected pre-flight. We also reported that there were 16 proteins identified with significant changes, i.e., increased in green or decreased in red, in expression levels found astronauts' plasma collected post-flight, in relation to those collected in-flight. Last January, we presented our results at the Annual NASA Human Research Program (HRP) workshop in Galveston. During the past year, we use Principal Component Analysis (PCA) to analyze these 453 unique and non-redundant proteins identified by LTQ Orbitrap XL Ion trap mass spectrometer. The PCA is frequently used in the global analysis of the "omic" datasets. It provides fully unsupervised information on the dominant directions of highest variability in the data and can, therefore, be used to investigate similarities between individual samples, or the formation of clusters. The PCA is a dimensionality reduction method used to reduce the dimensionality of large data sets by transforming a large set of variables into a smaller one while preserving as much information as possible. The new variables are called the principal components and they are linear combinations of the actual variables. The first principal component is a linear combination of all the actual variables that have maintained the greatest amount of variation. The second principal component is a linear combination of the remaining variables to give the second greatest amount of variation and this can continue for third, fourth, and so on components but usually the first and second components carry the most important information. A scatter plot of the first and second components (a score plot) will often display samples sharing similar characteristics being grouped together apart from samples with different characteristics (i.e., it shows clustering based on similarity). Another plot is also generated in this analysis called a loading plot. The loading plot shows how strongly each original variable influences the principal component. Often, most points in a loading plot will be clustered around the center and the outlier points may be associated with the variables making the largest contribution to the data variation. In summary, the PCA indicates the differences in the pattern of protein expression profiles between samples collected pre- and in-flight. Moreover, we constructed a heatmap to visualize the result of a hierarchical clustering calculation of the 14 proteins differentially expressed in samples collected at pre- or in-flight from each astronaut. The results from the heatmap show that the intensities (level of expression) of tropomodulin-3 (TMOD3), SERPINA7, SERPING1, and SERPRINC1 were higher in samples collected in-flight, in relation to those collected pre-flight. Notably, the protein in the SERPIN (serine protease inhibitor) family, i.e., SERPINA7, SERPINC1, and ISERPING1, is the majority of those with increased intensities (expression levels). However, the data also demonstrated individual variability in the intensities of these

	proteins. It should be noted that SERPIN protease inhibitors comprise a large family of molecules involved in inflammation, immune response, blood clotting, hormone transport, and complement activation, dementia, and tumorigenesis. Our heatmap data also showed high intensities of CP, FLG2, KRT2, F13A1, DMKN, LUM in samples collected pre-flight. Subsequently, the intensities of expression of these proteins were declined in samples collected in-flights. Likewise, the intensities of another set of proteins (i.e., CFB, FBLN1, AHSG, and ECM1) were high in samples collected pre-flight; this followed by a reduction in intensities in samples collected in-flight, with one exception of increased intensity of FBLN1 protein in sample4s collected mid-flight from one astronaut. Overall, the heatmap of our dataset demonstrated that the intensities of not only proteins in the SERPIN family but also TMOD3 (an actin filament pointed-end capping protein with multifunctional roles, including cell proliferation, cell migration, inflammation, and carcinogenesis) are consistently high in the in-flight samples. In contrast, low intensities of lumican (LUM) have been repeatedly detected in the in-flight samples. Of note, LUM is a major keratan sulfate proteoglycan of the cornea responsible for the circumferential growth, corneal transparency, epithelial cell migration, and tissue repair. Hence, it is possible to speculate that a reduction in LUM level may be associated with vision impairment that has been observed in many astronauts after spaceflight. In summary, our findings suggest that dysregulation of the SERPIN, TMOD3, and LUM may affect cell/tissue integrity and homeostasis, leading to late occurring health risks. Thus, our results may represent a foundation for the identification of countermeasures against the harmful effects of spaceflights.
Bibliography Type:	Description: (Last Updated: 03/27/2025)
Abstracts for Journals and Proceedings	Rithidech KN, Medococsa G, Crucian B, Martin D. "Impact of space flights on plasma proteome of astronauts." Presented at the 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. Abstracts. 2020 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020