Fiscal Year:	FY 2019	**Task Last Updated:**	FY 02/07/2019
PI Name:	Crucian, Brian Ph.D.		
Project Title:	Functional Immune Alterations, Latent Herpesvirus Reactivation, Physiological Stress, and Clinical Incidence Onboard the International Space Station		
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 Adverse Health Event Due to Altered Immune Response		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Organization Name:	NASA Johnson Space Center		
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City:	Houston	**State:**	TX
Zip Code:	77058-3607	**Congressional District:**	36
Comments:			
Project Type:	FLIGHT	**Solicitation / Funding Source:**	Directed Research
Start Date:	11/03/2014	**End Date:**	03/30/2020
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:	ISS		
Flight Assignment:	ISS NOTE: Extended to 3/30/2020 per PI (Ed., 2/7/19) NOTE: End date changed to 9/30/2019 due to revised research plan with Ground and Flight work, per HRP (Ed., 8/24/16) NOTE: Title change to "Functional Immune Alterations, Latent Herpesvirus Reactivation, Physiological Stress, and Clinical Incidence Onboard the International Space Station" per original proposal to HRP, per L. Milstead/HRP. Title on original information provided was "Innate and Adaptive Immune Function during Long-duration Spaceflight" (Ed., 8/23/16)		
Key Personnel Changes/Previous PI:	FEBRUARY 2019: 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 (NASA-JSC); 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" (U of Houston) solicited research; Dr. Kanokporn Rithidech's "Effects of Space Flights on the Proteome of Astronauts' Plasma" (SUNY) solicited research; and Dr. Honglu Wu's "DNA Damage in the ISS Astronaut's Lymphocytes and Their Association with Stress-Induced Immune Dysfunction" (NASA-JSC) solicited research.		

COI Name (Institution):	Pierson, Duane Ph.D. (NASA Johnson Space Center) Mehta, Satish Ph.D. (NASA Johnson Space Center/EASI) Stowe, Raymond Ph.D. (Microgen Labs) Wu, Honglu Ph.D. (NASA Johnson Space Center) Makedonas, George Ph.D. (JES Tech/NASA Johnson Space Center) Krieger, Stephanie B.S. (KBRWyle/NASA Johnson Space Center)
Grant/Contract No.:	Directed Research
Performance Goal No.:	
Performance Goal Text:	
Task Description:	UPDATED TASK DESCRIPTION/PROJECT RATIONALE FEBRUARY 2019: The Functional Immune project is a multi-disciplinary flight study whose purpose is to define comprehensively the immune system's response to long-duration spaceflight. There is a low -- but real -- incidence of infectious disease among crewmembers during spaceflight. Compared to ground controls, the incidence of latent herpesvirus reactivation is higher than expected. In addition, there is a consistent incidence of allergy and hypersensitivity symptoms; antihistamines remain the second-most prescribed medication onboard the International Space Station (ISS). Furthermore, data from flight studies suggest that during spaceflight astronauts exhibit persistent, low-level inflammation. All of these morbidities may be manifestations of altered immune function. However, the breadth of the perturbations throughout the human immune system, as well as their persistence during long-duration space missions, are unknown. If spaceflight impairs stably multiple aspects of the immune system, then it may confer a serious clinical risk to crewmembers for exploration-class missions. We hypothesize that while aspects of adaptive immune function are depressed during spaceflight, aspects of humoral or innate immune function may be unaltered or even sensitized. This would explain the observed reactivation of latent herpesviruses in astronauts, and also the elevated incidence of skin rashes and hypersensitivity reactions during International Space Station (ISS) missions. If the hypothesis is validated, it would be an important consideration for any future immunology countermeasures. For example, one would not give an immune 'booster' to address T cell function in a crewmember, if it might potentially worsen on-orbit skin rashes or allergy symptoms. We further hypothesize that there is a widely disparate post-landing recovery for various aspects of immune dysregulation following flight. Previous data have demonstrated that, surprisingly, ISS astronauts maintain shedding of latent herpesviruses at least to R+30. This study will fully characterize all relevant immune dysregulation through a post-mission recovery. The primary purpose of the study is to determine both acute and chronic alterations in crewmember immunobiology (both innate + adaptive parameters) in conjunction with relevant parameters from other disciplines (nutritional, radiation, virology, host-pathogen, stress, etc.). Parameters will be examined longitudinally in astronauts before, during, and following spaceflight. Post-flight assessments will be extended to determine the timecourse for full recovery of any dysregulated parameters. Specific Aim 1: To define longitudinally the functional capacity of adaptive and innate immune cells. For T cells, our endpoints are activation status and cytokine production; for Natural Killer (NK) cells, the endpoint is cytotoxic (killing) ability. Specific Aim 2: To determine the effect of spaceflight on a suite of soluble biomarkers that communicate in-vivo immune and physiological competence. From plasma, saliva, and urine we will quantify protein biomarkers of stress, inflammation, antimicrobial activity, and latent viral reactivation. Several solicited parameters will augment this aim, including proteomics and/or genomics. Specific Aim 3: To relate the immune profiles of astronauts to their clinical status, as well as to their habitual behavior in space: sleep/wake data, crew work schedules, surveys of in-flight symptomology and/or medication use (voluntary), vehicle docking/undocking, extravehicular activity (EVA). The results will inform NASA's scientific and operational communities about the influence on immunity of spaceflight-specific activity, factors we may modulate as part of an immune countermeasures strategy. The conclusions from this study will determine whether or not immune countermeasures will be necessary for exploration space missions. These data will define an immune surveillance strategy, comprehensive in its scope to encompass innate immunity, adaptive immunity, and relevant parameters from other disciplines, which will be critical to validate candidate countermeasures.
Rationale for HRP Directed Research:	Updated rationale August 2016: This research is directed because it contains highly constrained research, which requires focused and constrained data gathering and analysis. This new task is proposed as a directed/solicited study that will engage multiple external and/or international collaborators. Specific rationale for the directed portion of the study is included in the updated Task Description. Rationale Feb. 2015: This research is directed because it contains highly constrained research. In order to determine exact times of flight days and for the exact times in which the spacecraft cabin is depressed to 10.2 psia (thus creating the hypoxic condition), a researcher needs to have access to the Archive Data Retrieval (ADRIFT) subprogram inside of the Java Mission Evaluation Workstation System (JMEWS) which is only available on site here at Johnson Space Center, and requires proper clearance.
Research Impact/Earth Benefits:	The project will define a comprehensive immune system surveillance platform that may be applied to terrestrial immunologic investigations, including but not restricted to aging, primary and secondary immunodeficiency, and allergy.

Task Progress:	FEBRUARY 2019: The Functional Immune project benefits from a longitudinal sampling architecture, similar to the one that enabled the success of the Integrated Immune flight study previously. At every sampling time-point, we collect blood (ambient, live), saliva, and urine samples before, during, and following spaceflight. We powered the Functional Immune project to investigate 10 astronauts and 10 gender- and age- matched control subjects. Enrollment for this study began in 2016, and the first sampling time-point occurred in August of that year. To date, we have enrolled 11 astronauts and 10 ground control subjects. Unfortunately, due to the delay in launching the 57S expedition, the altered sampling timeframe for the inflight time-points does not conform to the experimental constraints of the study. Thus, we must drop from the study two of our enrolled astronauts who are aboard the 57S mission. We have replaced one of the crewmembers already, and recycled the associated control subject, since the gender and age are the same. Thus, we have nine crewmembers and nine ground control subjects towards our target of ten for each group. We expect to enroll the tenth study subject towards the end of 2019, and complete the sample collections during 2020. To date, six astronauts and their ground control subjects have completed their sampling regimen, seven time points. For two other crewmembers and their controls there remains only the last time-point outstanding. The ninth crewmember and associated control completed their pre-launch sampling time-points recently. The specimens from all the time-points we collected have been processed: samples of whole blood, plasma, and peripheral blood mononuclear cell (PBMC) were partitioned and sent to the external collaborators; plasma was isolated and cryopreserved for future cytokine analysis; immune cells were assayed for function and phenotype via flow cytometry; supernatants from 48 hr stimulation cultures were cryopreserved for future measurement of cytokine content. We analyzed the flow cytometry data at every time-point, but we have not synthesized them via longitudinal analysis. The virology lab processed the saliva and urine specimens at every time-point collected, performed the experiments to quantify stress hormones and latent virus reactivation, and recorded the data, but they have not synthesized them via longitudinal analysis. For the Microgen Laboratories work, PBMC samples have been cryopreserved; the samples will be batch-processed once all the time-points have been collected. Thus, we expect to receive data towards the end of 2019. Analysis of stimulated T cells through the use of confocal and electron microscopy from the completed subjects is also planned to begin soon.
Bibliography Type:	Description: (Last Updated: 09/15/2023)
Articles in Peer-reviewed Journals	Crucian BE, Choukèr A, Simpson RJ, Mehta S, Marshall G, Smith SM, Zwart SR, Heer M, Ponomarev S, Whitmire A, Frippiat JP, Douglas GL, Lorenzi H, Buchheim JI, Makedonas G, Ginsburg GS, Ott CM, Pierson DL, Krieger SS, Baecker N, Sams C. "Immune system dysregulation during spaceflight: Potential countermeasures for deep space exploration missions." Front Immunol. 2018 Jun 28;9:1437. Review. https://doi.org/10.3389/fimmu.2018.01437 ; PubMed PMID: 30018614; PubMed Central PMCID: PMC6038331 , Jun-2018
Articles in Peer-reviewed Journals	Makedonas G, Choukèr A, Mehta S, Simpson RJ, Stowe R, Sams C, Pierson D, Crucian B. "Mechanistic clues to overcome spaceflight-induced immune dysregulation." Curr Pathobiol Rep. 2018 Sep;6(3):185-92. Review. https://doi.org/10.1007/s40139-018-0178-6 , Sep-2018