Fiscal Year:	FY 2017	**Task Last Updated:**	FY 09/09/2016
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 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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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,Ground	**Solicitation / Funding Source:**	Directed Research
Start Date:	11/03/2014	**End Date:**	09/30/2019
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:**	
Contact Email:	Peter.norsk@nasa.gov		
Flight Program:	ISS		
Flight Assignment:	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:	August 2016: 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.		
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)		

Grant/Contract No.:	Directed Research
Performance Goal No.:	
Performance Goal Text:	
Task Description:	UPDATED TASK DESCRIPTION/PROJECT RATIONALE AUGUST 2016: This new task is proposed as a directed/solicited study that will engage multiple external and/or international collaborators. Specific rational for the directed portion of the study is as follows: Validated assays - requirement for technical homology: Some of the same measurements previously demonstrated to be dysregulated during long-duration spaceflight should be continued during the new study. It is important to correlate demonstrated areas of dysregulation in adaptive or viral parameters with new areas of investigation in the same individual subjects. Otherwise the result is separate data sets among which it is impossible to perform correlative analysis to determine mechanistic interactions. Many of these assays, as implemented during the Integrated Immune flight study, were developed and fully validated (and published) at Johnson Space Center (JSC). To solicit for assays would introduce additional and unnecessary cost and delay, as well as invite technical differences that could have a negative effect on data correlations. Validated sample processing protocols: For implementation of Integrated Immune, it was necessary to create and validate sample processing protocols (sample stability, storage conditions, methods to stain/fix/preserve, elimination of autofluorescence, etc.). In most cases, these requirements are unnecessary for terrestrial laboratories that do not deal with operational constraints. Terrestrial laboratories do not routinely analyze, nor do they even accept, aged samples. For example, sample preservation (cell, nucleic acid, culture products) must be stabilized to support IP participation. Requirement for established collaborations: We anticipate that validate assays from international partner flight studies would be necessary for the success of this proposal. The NASA JSC investigators have established both flight and ground collaborations with other US and International Partner immunologists. Rather than repeat flight studies sequentially, it is desirable to collaborate for the planned studies, so that all relevant in-flight assays may be performed. Examples include assays from the Salivary Markers, Immuno, MoCISS flight studies, as well as the CHOICE and NEEMO (NASA Extreme Environment Mission Operations project) analog studies. Implementation Aspects: For a complicated medical study with unique sampling constraints, the success of the Integrated Immune flight study has demonstrated the advantages of an in-house investigator component for study success. This is relevant to crew ICB, crew training, sample processing and distribution, and central coordination of sampling, sample sharing, maintenance of banked samples, sample storage for batch analysis, facilitation of data coordination for interpretative purposes, data coordination for report generation, interdisciplinary aspects (established linkages with Nutrition, Bone, Cardio disciplines, etc.), and interface with JSC flight surgeons, JSC data archives. Examples include Integrated Immune, where immune data are being coordinated with crew sleep/wake cycles and circadian misalignment, and the planning for the Salivary Markers flight study. Operational constraints-- Requirement for integrated and Immediate Sample Processing: The solicited aspects for this study will essentially be a very complicated sample sharing activity. All samples, including in-flight samples, must be processed at JSC, as JSC is the location where all BDC samples are collected, and where all in-flight samples return. In-flight samples will be at the end of their viability lifespan, by the time they are collected on-orbit, through hatch closure, deorbit, Soyuz return, and direct aircraft return to JSC. At this time, sample processing must occur without delay. Often, due to short (or otherwise sub optimal samples) real time judgment calls must be made to allow the maximal scientific return. We propose that to ensure mission success, the experienced JSC (directed) investigator team carry the integration responsibility for the entire team. The JSC staff has extensive experience regarding the integration required to support multiple immune investigators. For Integrated Immune, a study that also consisted of in-house and external collaborators (Mercer University, Microgen Laboratories, etc.), our suggested processing/implementation design worked well. For human subject samples, sampling volumes must be minimal, yet maximal assays must be generated on that product. JSC staff has processed ESA (European Space Agency) samples for both the NEEMO and Antarctica studies, and are knowledgeable regarding successfully integrating multiple IP studies on minimal sample. Outside investigators do not routinely work within this constraints. Cost and efficiency: Given the above requirements for assays, integration, sample processing, and that these unique and validated assays and sample processing protocols are in-place at JSC, it would introduce significant additional cost to 'train' an external lab perform these assays to the same fidelity. TASK DESCRIPTION NOVEMBER 2014: Some aspects of adaptive cellular immunity have been characterized during spaceflight, while many other areas of immunity (humoral, innate, cell specific functional, etc.) have not. The objective of this project is to characterize multiple diverse facets of immunoregulation during long-duration spaceflight. 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. Primary Aims: 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 scientific aims are as follows: 1. Longitudinally examine the effect of spaceflight on previously uninvestigated aspects of immunobiology including leukocyte distribution, various aspects of innate cellular function. Examined concurrently will be several previously validated assays of adaptive cellular distribution and function, to correlate within crewmembers both innate and adaptive

	immune dysregulation. 2. Examine the relationship in astronauts between immune function and various markers of in-vivo immune-physiological status, including plasma, salivary and urinary markers of stress, antimicrobial activity, and latent viral reactivation. Various solicited parameters are planned to augment this specific aim, including proteomics and/or genomics. Secondary Aims 3. Correlate findings of immune status with astronaut environmental, human, and stress factors such as sleep/wake data, crew work schedules, surveys of in-flight symptomology and/or medication use (voluntary), vehicle docking/undocking, extravehicular activity (EVA), etc. This correlative work should allow conclusions regarding environmental factors, which may potentially be modulated, on immune status. 4. Incorporate a final data analysis into specific conclusions regarding the immunobiology of spaceflight and conclusions regarding the necessity, lack thereof, or targeted aspects of, immune countermeasures for spaceflight. Develop a refined monitoring strategy encompassing innate immunity, adaptive immunity, and relevant parameters from other disciplines, which will be appropriate to validate 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:	
Task Progress:	Revised project implemented in 2016. 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.
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