Fiscal Year:	FY 2019	**Task Last Updated:**	FY 01/28/2020
PI Name:	Simpson, Richard Ph.D.		
Project Title:	Effects of Long-Term Exposure to Microgravity on Salivary Markers of Innate Immunity		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline--Element/Subdiscipline:			
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 (IRP Rev F)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	rjsimpson@email.arizona.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	713-397-0121
Organization Name:	University of Arizona		
PI Address 1:	College of Agriculture and Life Sciences; College of Medicine		
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PI Web Page:			
City:	Tucson	**State:**	AZ
Zip Code:	85721-0001	**Congressional District:**	3
Comments:	NOTE: Formerly at University of Houston until September 2017 move to University of Arizona.		
Project Type:	FLIGHT	**Solicitation / Funding Source:**	2010 Crew Health NNJ10ZSA003N
Start Date:	11/03/2011	**End Date:**	12/14/2018
No. of Post Docs:	1	**No. of PhD Degrees:**	2
No. of PhD Candidates:	5	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	
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:	ISS Flight Definition phase NOTE: End date changed to 12/14/2018 per NSSC information (Ed., 10/1/18) NOTE: End date changed to 5/2/2018 per NSSC information (Ed., 11/22/17) NOTE: End date changed to 11/2/2017 per NSSC information (Ed., 1/23/17) NOTE: End date changed to 11/2/2016 per NSSC information (Ed., 7/17/15) NOTE: Gap Immune05 deleted per IRP Rev E (Ed., 3/24/14)		
Key Personnel Changes/Previous PI:	September 2018 report: Dr. Satish Mehta has joined the project as CoInvestigator.		
COI Name (Institution):	Clarke, Mark Ph.D. (University of Houston) Crucian, Brian Ph.D. (Wyle Laboratories, Inc.) O'Connor, Dan Ph.D. (University of Houston) Pierson, Duane Ph.D. (NASA Johnson Space Center) Spielmann, Guillaume Ph.D. (University of Houston) Mehta, Satish Ph.D. (NASA Johnson Space Center)		
Grant/Contract No.:	NNX12AB48G		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	Immune system dysregulation has been documented during and after spaceflight, but it is not known if these changes increase infection susceptibility or pose a significant health risk to crewmembers. Inherent problems with current in-flight research are small sample sizes and the difficulty to control for the many confounding factors that impact on the immune system. As such, it is not known if changes in immunity are due to the microgravity environment per se, or to the stressors associated with landing and re-adaptation to the 1G environment. The present project proposes a Flight Definition investigation, utilizing a longitudinal repeated measures design to determine the effects of long-term exposure to microgravity on a host of salivary antimicrobial proteins (AMPs) associated with innate host immune defense, whilst also considering the impact of other acute stressors such as launch, Soyuz landing, and extravehicular activity (EVA). Saliva samples will be collected from crewmembers selected for International Space Station (ISS) mission and ground-based controls at bi-weekly intervals for 6 months prior to flight, during the 6-month period on the ISS, and for 1 month on return to Earth. Saliva sampling was selected because it is an excellent biological fluid with which to detect broad-spectrum biomarkers of front-line host immune defense and is suitable for the spaceflight environment. Attempts will also be made to establish relationships between AMPs and other stressors associated with spaceflight (i.e., mood state disturbances, circadian desynchronization, sleep loss/disruption, stress biomarkers) using serial data. Finally, blood samples will be collected before and after the mission to determine the impact of spaceflight on cellular aspects of innate immunity. Given the potential of salivary AMPs to serve as an indicator of weakened immunity during spaceflight, this project will serve as a foundation for future countermeasure developments and technological advances to detect real time changes during subsequent lunar or Mars missions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This project will improve our understanding on how acute and long-term stress impacts on multiple aspects of the immune system. These research findings will be useful to determine if any immune related health problems might exist in individuals exposed to stressful environments (i.e., soldiers, caregivers).
Task Progress:	The study was initiated in September 2012 and data collection started in March 2013. We enrolled the required number of subjects giving us a sample size of eight crewmembers and seven ground-based controls including a crewmember who completed a 1-year ISS mission. Baseline blood, urine, and saliva samples were collected from all crewmembers and ground-based control subjects. All crewmembers and ground-based controls successfully completed all experimental procedures, although compliance for the health survey questionnaires, Profile of Mood States (POMS), and Sleep Quality questionnaires was not complete. We successfully measured NK-cell killing potential against 4 separate tumor target cells in vitro and performed detailed immuophenotyping assays in whole blood samples identifying changes in the frequency of total T-cells, CD4+ T-cells, CD8+ T-cells, NK-cells, B-cells, granulocytes, monocytes, and their subtypes. In addition, interferon-gamma ELISpot assays were used to enumerate viral-specific T-cells against antigens derived from the herpesviruses cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), and Herpes simplex virus-1 (HSV-1). We also measured multiple analytes in saliva including the stress biomarkers alpha-amylase, cortisol and DHEA, the anti-microbial proteins LL-37, HNP 1-3, lactoferrinandlysozyme, and the systemic inflammatory marker C-reactive protein. We also quantified viral DNA against the latent herpesviruses CMV, EBV, VZV, and HSV-1 using both saliva and urine samples collected from the crew and the ground-based controls and measured IgG antibody titers against each of these viruses in plasma. The major findings from this project have so far been presented in three separate manuscripts. First, the NK-cell phenotypic and functional data was recently published in the Journal of Applied Physiology. The American Physiological Society (APS) selected this paper for a prestigious APS Select Award. Second, a manuscript with the salivary stress and antimicrobial biomarkers was recently submitted to Journal of Applied Physiology and is currently in review (Ed. note January 2020--the paper is published now; see Bibliography section). Third, the B-cell immune phenotyping data was combined with Dr. Guillaume Spielmann's omnibus project as we felt the story related to B-cell function would be better if it were combined with this data set. This manuscript was recently published in the Journal of Applied Physiology (PMID: 30496712). [Ed. note: compiled from PI's final report received October 2019]
Bibliography Type:	Description: (Last Updated: 08/04/2021)
Articles in Peer-reviewed Journals	Spielmann G, Agha NH, Kunz HE, Simpson RJ, Crucian BE, Mehta SK, Laughlin M, Campbell J. "B-cell homeostasis is maintained during long duration spaceflight." J Appl Physiol (1985). 2019 Feb 1;126(2):469-476. Epub 2018 Nov 29. https:// ; PubMed PMID: 30496712; PubMed Central PMCID: PMC6397409. , Feb-2019
Articles in Peer-reviewed Journals	Agha NH, Baker FL, Kunz HE, Spielmann G, Mylabathula PL, Rooney BV, Mehta SK, Pierson DL, Laughlin MS, Markofski MM, Crucian BE, Simpson RJ. "Salivary antimicrobial proteins and stress biomarkers are elevated during a 6-month mission to the International Space Station." J Appl Physiol (1985). 2019 Nov 21. [Epub ahead of print] PubMed PMID: 31751178 ; https:// , Nov-2019
Articles in Peer-reviewed Journals	Bigley AB, Agha NH, Baker FL, Spielmann G, Kunz HE, Mylabathula PL, Rooney B, Laughlin MS, Pierson DL, Mehta SK, Crucian BE, Simpson RJ. "NK-cell function is impaired during long-duration spaceflight." J Appl Physiol (1985). 2019 Apr 1;126(4):842-53. Epub 2018 Nov 1. PubMed PMID: 30382809 ; https:// , Apr-2019
Articles in Peer-reviewed Journals	Agha NH, Mehta SK, Rooney BV, Laughlin MS, Markofski MM, Pierson DL, Katsanis E, Crucian BE, Simpson RJ. "Exercise as a countermeasure for latent viral reactivation during long duration space flight." FASEB J. First published: 03 January 2020. https:// ; PubMed PMID: 31908052 , Jan-2020

Articles in Peer-reviewed Journals	Kunz HE, Agha NH, Hussain M, LaVoy EC, Smith KA, Mylabathula P, Diak D, Baker FL, O'Connor DP, Bond RA, Katsanis E, Bollard CM, Simpson RJ. "The effects of ß1 and ß1+2 adrenergic receptor blockade on the exercise-induced mobilization and ex vivo expansion of virus-specific T cells: Implications for cellular therapy and the anti-viral immune effects of exercise." Cell Stress Chaperones. Published online ahead of print 10 August 2020. https:// ; PMID: 32779001 , Aug-2020
Awards	Bigley AB, Agha NH, Baker FL, Spielmann G, Kunz HE, Mylabathula PL, Rooney B, Laughlin MS, Pierson DL, Mehta SK, Crucian BE, Simpson RJ. "American Physiological Society (APS) selected this paper for a prestigious APS Select Award, "For distinction in scholarship in the Journal of Applied Physiology for the article 'NK-cell function is impaired during long-duration spaceflight.' " https:// , January 2019." Jan-2019