

<b>Fiscal Year:</b>	FY 2018	<b>Task Last Updated:</b>	FY 09/03/2018
<b>PI Name:</b>	Simpson, Richard Ph.D.		
<b>Project Title:</b>	Effects of Long-Term Exposure to Microgravity on Salivary Markers of Innate Immunity		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	HUMAN RESEARCH		
<b>Program/Discipline--Element/Subdiscipline:</b>			
<b>Joint Agency Name:</b>		<b>TechPort:</b>	No
<b>Human Research Program Elements:</b>	(1) <b>HHC</b> :Human Health Countermeasures		
<b>Human Research Program Risks:</b>	(1) <b>Immune</b> :Risk of Adverse Health Event Due to Altered Immune Response (IRP Rev F)		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Zip Code:</b>	85721-0001	<b>Congressional District:</b>	3
<b>Comments:</b>	NOTE: Formerly at University of Houston until September 2017 move to University of Arizona.		
<b>Project Type:</b>	FLIGHT	<b>Solicitation / Funding Source:</b>	2010 Crew Health NNJ10ZSA003N
<b>Start Date:</b>	11/03/2011	<b>End Date:</b>	12/14/2018
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	2
<b>No. of PhD Candidates:</b>	5	<b>No. of Master' Degrees:</b>	0
<b>No. of Master's Candidates:</b>	0	<b>No. of Bachelor's Degrees:</b>	
<b>No. of Bachelor's Candidates:</b>	0	<b>Monitoring Center:</b>	NASA JSC
<b>Contact Monitor:</b>	Vos, Jessica	<b>Contact Phone:</b>	
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<b>Flight Program:</b>	ISS		
<b>Flight Assignment:</b>	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)		
<b>Key Personnel Changes/Previous PI:</b>	September 2018 report: Dr. Satish Mehta has joined the project as CoInvestigator.		
<b>COI Name (Institution):</b>	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 )		
<b>Grant/Contract No.:</b>	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:**

Project objectives for the last reporting period were:

1. Complete all data collection procedures for 8 crewmembers (including 1y mission) and 7 ground-based control subjects.
2. Continue analysis of archived samples for all enrolled subjects.
3. Disseminate research findings to the scientific community.

Overview of Work Completed Study Progress: The study was initiated in September 2012 and data collection started in March 2013. We successfully enrolled the required number of subjects giving us a sample size of eight crewmembers and seven ground-based controls including an additional crewmember who completed a 1-year mission to the ISS. Baseline blood, urine, and saliva samples have been collected from all crewmembers and ground-based control subjects. All crewmembers and ground-based controls have completed all experimental procedures. We have obtained in flight samples and ambient blood returns from all enrolled crewmembers. All baseline and in flight ambient blood samples were processed and analyzed successfully. Frozen saliva, urine, and plasma samples have all been processed and analyzed. The IRB (Institutional Review Board) protocol was renewed in July 2018. During the last reporting period, the project team have been analyzing and interpreting data in preparation for dissemination to the scientific community. Data analysis and write up was somewhat delayed due to the Principal Investigator (PI) Dr. Simpson changing institutions (moving from the University of Houston to the University of Arizona) within the last reporting period. One scientific paper was published during the last reporting period, two others have been submitted for publication, and two others are currently in preparation (details below). One of the recent articles from this work "Long-duration spaceflight impairs NK-cell function" is currently under review with the Journal of Applied Physiology. Publications and Presentations: Our validation work for this project allowed us to assess NK-cell function in the context of latent cytomegalovirus infection, age, and exercise. This led to publications by Bigley et al. (2016) in the journals Cellular Immunology and Clinical and Experimental Immunology, Bigley et al. (2015) in Oxidative Medicine and Cellular Longevity and Brain, Behavior, and Immunity, and Bigley et al. (2018) in Clinical and Experimental Immunology. We also published a manuscript in European Journal of Applied Physiology, which stemmed from the validation work of our saliva assays for this project (Kunz et al., 2015). In addition, Spielmann et al. (2016) and Kunz et al. (2018) used the validation work from the viral T-cell quantification component of the "Salivary Markers" study for a publication in Scientific Reports and Physiology and Behavior, respectively. Furthermore, Graff et al. (2018), Agha et al. (2018), and LaVoy et al. (2017) used the validation work for cellular phenotyping of the "Salivary Markers" study in their recent publications in Brain, Behavior, and Immunity and Physiological Reports. The PI (Dr. Simpson) collaborated with NASA scientists and other space life scientists to generate two review articles pertaining to the effects of space travel on immune function (Crucian et al. 2018; Makedonas et al., 2018). Hematology data from this project was also used in the BMC Hematology publication by Kunz et al. (2017). NASA funding was acknowledged in all of these publications. The work supported by this research grant was presented at the International Society of Exercise and Immunology (ISEI) 2017 Symposium in July 2017, the Human Research Program Investigators' Workshop in January 2017 and February 2018, and the American College of Sports Medicine (ACSM) annual meetings in 2017 and 2018. Current and Future Work

All data has been collected and analyzed. The following papers are a direct result of this project and have been published (See also Cumulative Bibliography): Crucian BE, Chouker A, Simpson RJ, Mehta S, Marshall G, Smith SM, Zwart SR, Heer M, Ponomarev S, Whitmire A, Fripiat JP, Douglas GL, Lorenzi H, Buchheim JI, Makedonas G, Ginsburg GS, Ott CM, Pierson DL, Krieger SS, Baecker N & Sams C (2018). Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions. *Frontiers in Immunology*, 9, 1437. Crucian, B., Simpson, R.J., Mehta, S., Stowe, R., Chouker, A., Hwang, S., Actor, J.K., Salam, A.P., Pierson, D. and C. Sams. (2014) Terrestrial stress analogs for spaceflight associated immune system dysregulation. *Brain, Behavior and Immunity*, 39, 23-32.

Kunz H, Quiariarte H, Simpson RJ, Ploutz-Snyder R, McMonigal K, Sams C & Crucian B. (2017). Alterations in hematologic indices during long-duration spaceflight. *BMC Hematology*, 8, 17-12. Makedonas G, Chouker A, Mehta S,

	<p>Simpson RJ, Stowe R, Sams C, Pierson DL &amp; Crucian BE (2018). Mechanistic Clues to Overcome Spaceflight-Induced Immune Dysregulation. <i>Current Pathobiology Reports</i>, 6, 185-192. Spielmann, G., Laughlin, M. S., Kunz, H., Crucian, B. E., Quiriarte, H. D., Mehta, S. K., Pierson, D. L. &amp; Simpson, R. J. (2018). Latent viral reactivation is associated with changes in plasma antimicrobial protein concentrations during long-duration spaceflight. <i>Acta Astronautica</i>, 146, 111-116.</p> <p>The following manuscripts have been submitted for publication or are in preparation:</p> <p>Bigley, A.B., Agha, N.H., Kunz, H.E., Baker, F.L., Spielmann, G., Rooney, B.V., Mylabathula, P., Laughlin, M. S., Mehta, S. K., Pierson, D. L. Crucian, B. E., &amp; Simpson, R. J. (2018). NK-cell function is impaired during long duration spaceflight. <i>Journal of Applied Physiology</i> (In Review).</p> <p>Spielmann, G., Simpson, R. J. Laughlin, M. S., Kunz, H., Crucian, B. E., Mehta, S. K. &amp; Campbell, J.C. (2018). B-cell homeostasis is maintained during long-duration spaceflight. <i>Journal of Applied Physiology</i> (In Review).</p> <p>Agha, N.H., Kunz, H.E., Baker, F.L., Spielmann, G., Rooney, B.V., Mylabathula, P., Bigley, A.B., Laughlin, M. S., Mehta, S. K., Pierson, D. L. Crucian, B. E., &amp; Simpson, R. J. (2018). Long-duration spaceflight alters antimicrobial proteins in astronaut saliva (In preparation).</p> <p>Agha, N.H., Spielmann, G., Kunz, H.E., Baker, F.L., Rooney, B.V., Mylabathula, P., Bigley, A.B., Laughlin, M. S., Mehta, S. K., Pierson, D. L. Crucian, B. E., &amp; Simpson, R. J. (2018). T-cell and NK-cell responses to latent viral reactivation onboard the International Space Station (In preparation).</p>
<b>Bibliography Type:</b>	Description: (Last Updated: 08/04/2021)
<b>Abstracts for Journals and Proceedings</b>	<p>Agha NH, Spielmann G, Kunz HE, Baker FL, Rooney BV, Mylabathula P, Bigley AB, Laughlin MS, Mehta SK, Pierson DL, Crucian BE, Simpson RJ. "The impact of a 6-month mission to the International Space Station (ISS) on salivary antimicrobial proteins." 13th International Society for Exercise and Immunology (ISEI) Symposium, Coimbra, Portugal, July 11-14, 2017.  <i>Annals of Research in Sport and Physical Activity</i>. 2018;ex2018:97-8. <a href="https://">https://</a>, Jul-2017</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Bigley AB, Mylabathula PL, Agha N, Li L, Mehta S, Crucian B, Pierson D, Laughlin M, Rezvani K, Simpson RJ. "The role of microgravity in dysregulated NK-cell function and CMV-specific T-cell responses during spaceflight." 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017.  2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. , Jan-2017</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Bigley AB, Agha NH, Kunz HE, Baker FL, Spielmann G, Rooney BV, Mylabathula P, Laughlin MS, Mehta SK, Pierson DL, Crucian BE, Simpson RJ. "Dysregulated NK-cell function during long-duration spaceflight." 13th International Society for Exercise and Immunology (ISEI) Symposium, Coimbra, Portugal, July 11-14, 2017.  <i>Annals of Research in Sport and Physical Activity</i>. 2018;ex2018:99-100. <a href="https://">https://</a>, Jul-2017</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Simpson RJ, Bigley AB, Spielmann G, Kunz H, Agha N, Baker F, Rooney B, Mylabathula PL, Graff R, Laughlin M, Mehta S, Pierson D, Crucian B. "Long duration spaceflight impairs NK-cell function in ISS crewmembers: findings from the 'Salivary Markers' project." 2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017.  2017 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 23-26, 2017. , Jan-2017</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Bigley AB, Agha NH, Kunz HE, Baker FL, Spielmann G, Rooney BV, Mylabathula P, Laughlin MS, Mehta SK, Pierson DL, Crucian BE, Simpson RJ. "The role of microgravity and stress-related humoral factors in dysregulated NK-cell function during spaceflight." National Space Biomedical Research Institute (NSBRI) Summer Bioastronautics Institute, Houston, TX, USA, May 31-June 3, 2016.  National Space Biomedical Research Institute (NSBRI) Summer Bioastronautics Institute, Houston, TX, USA, May 31-June 3, 2016. , Jun-2016</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Bigley AB, Agha NH, Kunz HE, Baker FL, Spielmann G, Mylabathula PL, Bigley AB, Simpson RJ. "Simulated microgravity 'disarms' human NK-cells and inhibits cytotoxicity." 2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016.  2016 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 8-11, 2016. , Feb-2016</p>
<b>Abstracts for Journals and Proceedings</b>	<p>Spielmann G, Campbell J, Crucian BE, Laughlin MS, Simpson RJ. "The impact of long-duration spaceflight on the function of plasma cells." American College of Sports Medicine (ACSM) 65th Annual Meeting, Minneapolis, MN, May 29-June 2, 2018.  <i>Medicine &amp; Science in Sports &amp; Exercise</i>. 2018 May;50(Suppl 1 5S):336. <a href="https://">https://</a>, Jun-2018</p>
<b>Articles in Peer-reviewed Journals</b>	<p>Bigley AB, Baker FL, Simpson RJ. "Cytomegalovirus: an unlikely ally in the fight against blood cancers?" <i>Clin Exp Immunol</i>. 2018 Sep;193(3):265-74. <a href="https://">https://</a>; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/29737525/">PMID: 29737525</a>; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC6150251/">PMCID: PMC6150251</a>, Sep-2018</p>
<b>Articles in Peer-reviewed Journals</b>	<p>Simpson RJ, Graham SM, Connaboy C, Clement R, Pollonini L, Florida-James GD. "Blood lactate thresholds and walking/running economy are determinants of backpack-running performance in trained soldiers." <i>Appl Ergon</i>. 2017 Jan;58:566-72. Epub 2016 May 4. <a href="https://">https://</a>; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/27154276/">PMID: 27154276</a>, Jan-2017</p>
<b>Articles in Peer-reviewed Journals</b>	<p>Agha NH, Baker FL, Kunz HE, Graff R, Azadan R, Dolan C, Laughlin MS, Hosing C, Markofski MM, Bond RA, Bollard CM, Simpson RJ. "Vigorous exercise mobilizes CD34+ hematopoietic stem cells to peripheral blood via the B2-adrenergic receptor." <i>Brain Behav Immun</i>. 2018 Feb;68:66-75. Epub 2017 Oct 7. <a href="https://">https://</a>; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/29017969/">PMID: 29017969</a>, Feb-2018</p>
<b>Articles in Peer-reviewed Journals</b>	<p>Alfano CA, Bower J, Cowie J, Lau S, Simpson RJ. "Long-duration space exploration and emotional health: Recommendations for conceptualizing and evaluating risk." <i>Acta Astronaut</i>. 2018 Jan;142:289-99. <a href="https://">https://</a>, Jan-2018</p>

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." <i>Front Immunol.</i> 2018 Jun 28;9:1437. Review. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/30018614/">PMID: 30018614</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC6038331/">PMCID: PMC6038331</a> , Jun-2018
Articles in Peer-reviewed Journals	Graff RM, Kunz HE, Agha NH, Baker FL, Laughlin M, Bigley AB, Markofski MM, LaVoy EC, Katsanis E, Bond RA, Bollard CM, Simpson RJ. "β2-adrenergic receptor signaling mediates the preferential mobilization of differentiated subsets of CD8+ T-cells, NK-cells and non-classical monocytes in response to acute exercise in humans." <i>Brain Behav Immun.</i> Available online 30 August 2018, In Press, Corrected Proof. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/30172948/">PMID: 30172948</a> , Aug-2018
Articles in Peer-reviewed Journals	Kunz H, Quiariarte H, Simpson RJ, Ploutz-Snyder R, McMonigal K, Sams C, Crucian B. "Alterations in hematologic indices during long-duration spaceflight." <i>BMC Hematol.</i> 2017 Sep 8;17:12. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/28904800/">PMID: 28904800</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC5590186/">PMCID: PMC5590186</a> , Sep-2017
Articles in Peer-reviewed Journals	Kunz HE, Spielmann G, Agha NH, O'Connor DP, Bollard CM, Simpson RJ. "A single exercise bout augments adenovirus T-cell mobilization and function." <i>Physiol Behav.</i> 2018 Oct 1;194:56-65. Epub 2018 Apr 30. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/29723594/">PMID: 29723594</a> , Oct-2018
Articles in Peer-reviewed Journals	LaVoy EC, Hussain M, Reed J, Kunz H, Pistillo M, Bigley AB, Simpson RJ. "T-cell redeployment and intracellular cytokine expression following exercise: Effects of exercise intensity and cytomegalovirus infection." <i>Physiol Rep.</i> 2017 Jan;5(1): e13070. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/28087817/">PMID: 28087817</a> ; PubMed Central <a href="https://pubmed.ncbi.nlm.nih.gov/PMC5256156/">PMCID: PMC5256156</a> , Jan-2017
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." <i>Curr Pathobiol Rep.</i> 2018 Jul 19;6:185-92. Review. <a href="https://">https://</a> , Jul-2018
Articles in Peer-reviewed Journals	Rooney BV, Bigley AB, LaVoy EC, Laughlin M, Pedlar C, Simpson RJ. "Lymphocytes and monocytes egress peripheral blood within minutes after cessation of steady state exercise: A detailed temporal analysis of leukocyte extravasation." <i>Physiol Behav.</i> 2018 Oct 1;194:260-7. Epub 2018 Jun 7. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/29885920/">PMID: 29885920</a> , Oct-2018
Articles in Peer-reviewed Journals	Simpson RJ, Bigley AB, Agha N, Hanley PJ, Bollard CM. "Mobilizing immune cells with exercise for cancer immunotherapy." <i>Exerc Sport Sci Rev.</i> 2017 Jul;45(3):163-72. Review. <a href="https://">https://</a> ; PubMed <a href="https://pubmed.ncbi.nlm.nih.gov/28418996/">PMID: 28418996</a> , Jul-2017
Articles in Peer-reviewed Journals	Spielmann G, Laughlin MS, Kunz H, Crucian BE, Quiariarte HD, Mehta SK, Pierson DL, Simpson RJ. "Latent viral reactivation is associated with changes in plasma antimicrobial protein concentrations during long-duration spaceflight." <i>Acta Astronaut.</i> 2018 May;146:111-6. <a href="https://">https://</a> , May-2018