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| **Fiscal Year:** | FY 2015 | **Task Last Updated:** | FY 10/29/2014 |
| **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 | | |
| **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 | | |
| **PI Address 2:** | 1177 E. Fourth Street, Room 308, Shantz Building | | |
| **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:** | 11/02/2017 |
| **No. of Post Docs:** | 3 | **No. of PhD Degrees:** | 2 |
| **No. of PhD Candidates:** | 6 | **No. of Master' Degrees:** | |
| **No. of Master's Candidates:** | 1 | **No. of Bachelor's Degrees:** | |
| **No. of Bachelor's Candidates:** | 0 | **Monitoring Center:** | NASA JSC |
| **Contact Monitor:** | Vos, Jessica | **Contact Phone:** | |
| **Contact Email:** | jessica.r.vos@nasa.gov | | |
| **Flight Program:** | ISS | | |
| **Flight Assignment:** | ISS Flight Definition phase<br>NOTE: End date changed to 11/2/2017 per NSSC information (Ed., 1/23/17)<br>NOTE: End date changed to 11/2/2016 per NSSC information (Ed., 7/17/15)<br>NOTE: Gap Immune05 deleted per IRP Rev E (Ed., 3/24/14) | | |
| **Key Personnel Changes/Previous PI:** | | | |
| **COI Name (Institution):** | Clarke, Mark Ph.D. ( University of Houston )<br>Crucian, Brian Ph.D. ( Wyle Laboratories, Inc. )<br>Lowder, Thomas Ph.D. ( University of Houston )<br>O'Connor, Dan Ph.D. ( University of Houston )<br>Pierson, Duane Ph.D. ( NASA Johnson Space Center )<br>Spielmann, Guillaume Ph.D. ( University of Houston ) | | |
| **Grant/Contract No.:** | NNX12AB48G | | |
| **Performance Goal No.:** | | | |
| **Performance Goal Text:** | | | |

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| **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 EVA. Saliva samples will be collected from crewmembers selected for 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.<br>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 Summary<br>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 Flight Definition investigation will utilize a longitudinal repeated measures design to determine the effects of long-term exposure to microgravity on a host of salivary antimicrobial proteins (AMPs), latent viral reactivation, antibacterial properties of saliva, and blood markers associated with innate host immune defense, whilst also considering the impact of other acute stressors such as Soyuz landing. Saliva, urine, and blood samples will be collected from crewmembers selected for ISS mission and ground-based controls pre-flight (L-180-L-45), At “early”, “mid,” and “late” phases during the 6-month period on the ISS, and up to R+63 on return to Earth. Saliva sampling was selected as the primary source 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 salivary and cellular immune markers, viral reactivation and other stressors associated with spaceflight (i.e. mood state disturbances, circadian desynchronization, sleep loss/disruption, stress biomarkers) using serial data. Blood samples will be used for monocyte, NK-cell, and neutrophil phenotype and functional assays. This project will help to establish if spaceflight alters innate immune function, which is important to determine if altered immunity poses a significant risk of an adverse health event among crewmembers. Moreover, these data will serve as a foundation for future countermeasure developments and technological advances to detect real time changes in immune function during subsequent lunar or Mars missions.<br><br>Task Objective/Description<br><br>Year 3 objectives for this project were:<br><br>1. Continue test subject recruitment and complete all data collection procedures for 1 crewmember and 1 ground-based control subject; 2. Continue experimental procedures for all enrolled subjects; 3. Disseminate research findings to the scientific community.<br><br>Overview of Work Completed in Year 3<br><br>Study Progress: The study was initiated in September 2012 and data collection started in March 2013. As of October 2014, we have enrolled the required number of subjects giving us a sample size of six crewmembers and six ground-based controls. We also recruited a crewmember on the 1-year ISS mission and will continue to obtain samples from this subject into FY16. Baseline blood, urine, and saliva samples have been collected from all crewmembers and ground-based control subjects. One crewmember has completed all experimental procedures and a second crewmember has one remaining sample to provide before completing the entire protocol (this is currently scheduled for November 2014). We have obtained in flight samples and ambient blood returns from a total of three crewmembers to date. All baseline and in flight ambient blood samples were processed and analyzed successfully. Saliva, urine, and blood plasma samples have been stored at -80°C until analysis. Frozen samples will be analyzed on completion of the study protocol. The IRB protocol was renewed in July 2014.<br><br>Publications and Presentations:<br><br>Dr. Crucian and Dr. Simpson took the lead on compiling a review article focused on terrestrial analogs of spaceflight-induced immune system dysregulation. The manuscript entitled: “Terrestrial Stress Analogs for Spaceflight Associated Immune System Dysregulation” was published in Brain, Behavior and Immunity in July 2014 (Crucian, Simpson et al. 2014). The paper by Bigley et al. in which we developed the NK-cell functional assay for use in this study, was also published in Brain, Behavior and Immunity in July 2014 (Bigley, Rezvani et al. 2014). Our validation work for this project also allowed us to assess NK-cell function in the context of latent cytomegalovirus infection. This led to a submitted manuscript that is currently under review with the Journal of Immunology. We also submitted a manuscript to European Journal of Applied Physiology, which stemmed from the validation work of our saliva assays for this project (Kunz et al). This paper has been accepted subject to minor revisions. NASA funding was acknowledged |

in all of these publications. The work supported by this research grant was presented at the Human Research Program Investigator's Workshop in February 2014 and the Psychoneuroimmunology Research Society Symposium in July 2014.

Current and Future Work

The study protocol is ongoing. By the end of year 4 we expect to have 4 crewmembers complete the entire experimental protocol. The current Soyuz schedule for our enrolled subjects means we will have to extend the project into a fifth year. This is required not only to complete the experimental procedures for the 'Salivary Markers' subjects, but also for the subject on the 1-year ISS mission. The 1-year mission subject is currently scheduled to return in March 2016 and our protocol requirements include the collection of biological samples up to 66 days after landing. Based on the current 'Salivary Markers' crewmember enrollment and Soyuz schedule, we expect to collect our final samples by May 2016 (45S). The remainder of FY16 will be spent analyzing frozen biological samples, interpreting data and producing scientific papers.

Bibliography

The following published papers (and papers in revision) were supported by this work:

Bigley, A. B., K. Rezvani, C. Chew, T. Sekine, M. Pistillo, B. Crucian, C. M. Bollard and R. J. Simpson (2014). "Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells." Brain Behav Immun 39: 160-171.

Bigley A.B., Rezvani K., Shah N., Sekine T., Spielmann G., Pistillo M., Agha N., Kunz H., LaVoy E.C.P., Bollard C.M., Simpson R.J. "Latent CMV infection enhances anti-tumor cytotoxicity through accumulation of NKG2C+ NK-cells in healthy humans". J Immunol (In Review, submitted September 2014).

Crucian, B., R. J. Simpson, S. Mehta, R. Stowe, A. Chouker, S. A. Hwang, J. K. Actor, A. P. Salam, D. Pierson and C. Sams (2014). "Terrestrial stress analogs for spaceflight associated immune system dysregulation." Brain Behav Immun 39: 23-32.

Kunz, H. Bishop, N.C., Spielmann, G., Pistillo, M., Reed, J., Ograjsek, T., Park, Y., Mehta, S., Pierson, D.L. and R.J. Simpson. "Fitness level impacts salivary antimicrobial responses to a single bout of cycling exercise". Eur J Appl Physiol (In Revision, submitted July 2014)

The following presentations were delivered and supported by this work:

Bigley, A.B., G. Spielmann, E. C. LaVoy, M. Pistillo, H. Kunz, N. Agha, R. J. Simpson. "Latent cytomegalovirus infection enhances baseline anti-tumor cytotoxicity but impairs NK-cell responses to acute exercise through preferential expansion of NKG2C+ NK-cells in healthy humans". Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, USA, May 28th -31st 2014.

Kunz, H., G. Spielmann, M. Pistillo, J. Reed, T. Ograjsek, R. J. Simpson. "The impact of workload and training status on salivary antimicrobial proteins following acute exercise". Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, USA, May 28th -31st 2014.

Spielmann, G., A. B. Bigley, B. E. Crucian, S. Mehta, D. Pierson, H. Kunz, N. Agha, E. C. LaVoy and R. J. Simpson. "Immune cell phenotypes and NK-cell function in astronauts and controls 5 months before a 6-month mission to the International Space Station". Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, USA, May 28th -31st 2014.

Spielmann, G. B. E. Crucian, S. Mehta, H. Kunz, D. Pierson, and R. J. Simpson. "The impact of long-duration spaceflight on plasma antimicrobial proteins". NASA Human Research Program Investigator's Workshop, Galveston, TX, USA, Feb 12th - 13th 2013.

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| **Bibliography Type:** | Description: (Last Updated: 09/27/2023) |
| **Abstracts for Journals and Proceedings** | Bigley AB, Spielmann G, LaVoy EC, Pistillo M, Kunz H, Agha N, Simpson RJ. "Latent cytomegalovirus infection enhances baseline anti-tumor cytotoxicity but impairs NK-cell responses to acute exercise through preferential expansion of NKG2C+ NK-cells in healthy humans." 2014 Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, May 28t-31, 2014.<br>Brain, Behavior, and Immunity. 2014 Sep;40 Suppl:e44. http://dx.doi.org/10.1016/j.bbi.2014.06.173 , Sep-2014 |
| **Abstracts for Journals and Proceedings** | Kunz H, Spielmann G, Pistillo M, Reed J, Ograjsek T, Simpson RJ. "The impact of workload and training status on salivary antimicrobial proteins following acute exercise." 2014 Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, May 28t-31, 2014.<br>Brain, Behavior, and Immunity. 2014 Sep;40 Suppl:e26. http://dx.doi.org/10.1016/j.bbi.2014.06.108 , Sep-2014 |
| **Abstracts for Journals and Proceedings** | Spielmann G, Bigley AB, Crucian B, Mehta S, Pierson D, Kunz S, Agha N, LaVoy C, Simpson RJ. "Immune cell phenotypes and NK-cell function in astronauts and controls 5 months before a 6-month mission to the International Space Station." 2014 Psychoneuroimmunology Research Society Annual Meeting, Philadelphia, PA, May 28t-31, 2014.<br>Brain, Behavior, and Immunity. 2014 Sep;40 Suppl:e51. http://dx.doi.org/10.1016/j.bbi.2014.06.196 , Sep-2014 |
| **Abstracts for Journals and Proceedings** | Spielmann G, Crucian B, Mehta S, Kunz S, Pierson D, Simpson RJ. "The impact of long-duration spaceflight on plasma antimicrobial proteins." 2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014.<br>2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014.<br>http://www.hou.usra.edu/meetings/hrp2014/pdf/3170.pdf , Feb-2014 |
| **Articles in Peer-reviewed Journals** | Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, Bollard CM, Simpson RJ. "Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells." Brain Behav Immun. 2014 Jul;39:160-71. Epub 2013 Nov 5.<br>http://dx.doi.org/10.1016/j.bbi.2013.10.030 ; PubMed PMID: 24200514 , Jul-2014 |

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| **Articles in Peer-reviewed Journals** | Crucian B, Simpson RJ, Mehta S, Stowe R, Chouker A, Hwang SA, Actor JK, Salam AP, Pierson D, Sams C. "Terrestrial stress analogs for spaceflight associated immune system dysregulation." Brain Behav Immun. 2014 Jul;39:23-32. Epub 2014 Jan 24. http://dx.doi.org/10.1016/j.bbi.2014.01.011 ; PubMed PMID: 24462949 , Jul-2014 |