Fiscal Year:	FY 2017	**Task Last Updated:**	FY 07/18/2017
PI Name:	Bigley, Austin Ph.D.		
Project Title:	The Role of Microgravity and Stress-related Humoral Factors in Dysregulated NK-cell Function during Spaceflight		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Radiation Effects Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	77204-6015	**Congressional District:**	18
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2015 NSBRI-RFA-15-01 First Award Fellowships
Start Date:	10/01/2015	**End Date:**	03/31/2017
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**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:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 3/31/2017 (previously 5/31/2017) per NSBRI (Ed., 4/1/17) NOTE: End date changed to 5/31/2017 (previously 9/30/2016) per NSBRI (Ed., 12/27/16)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Simpson, Richard (MENTOR/ University of Houston)		
Grant/Contract No.:	NCC 9-58-PF04307		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Before we can ethically send Astronauts to distant locations in space, such as Mars or asteroids, it is critical that we understand how spaceflight affects the human immune system. For years, post-flight data has suggested that spaceflight has a negative impact on the immune system. Unfortunately, the majority of this data was obtained following short-duration missions after the Astronauts had returned to Earth, meaning that no in-flight data was collected. The recent 'Integrated Immune' study filled many of these knowledge gaps by analyzing blood obtained from Astronauts on the Space Shuttle (or International Space Station (ISS)) while they were still in space. Of particular interest were the findings that anti-viral immune responses were compromised during spaceflight. Consequently, latent viral reactivation can result in many negative consequences including Shingles, reduced vaccine efficacy, and increased susceptibility to infection. While the 'Integrated Immune' study focused primarily on the adaptive immune system, our 'Salivary Markers' flight experiment (Principal Investigator Dr. Richard Simpson) has focused on the innate immune system. The current proposal focuses on Natural Killer (NK)-cells, which are able to kill virally-infected and malignant cells without prior exposure. Our in-flight data shows that NK-cell anti-tumor activity is greatly reduced during spaceflight, while cytomegalovirus (CMV)-driven responses are amplified. The current proposal will explore two plausible mechanisms for these observations--microgravity and stress. The effects of microgravity can be simulated with a rotating wall vessel that keeps the cells in a constant state of freefall, while stress can be simulated using serum (with natural stress hormones) from Astronauts on ISS. It is hypothesized that treatment with simulated microgravity and spaceflight-derived serum will mimic the deleterious effects of spaceflight on NK-cells. Once we have determined the mechanisms underpinning the adverse effects of spaceflight on NK-cells, we can begin to develop countermeasures that will protect future space explorers from becoming immunocompromised during long-duration missions. Based on data from 10 subjects tested so far, we are able to report that exposure to simulated microgravity (SMG) decreases NK-cell anti-tumor activity similarly to spaceflight. This decrease in function was due to impaired NK-cell degranulation, decreased production of cytotoxic cytokines (e.g., tumor necrosis factor-a and interferon-a), and reduced expression of the cytolytic protein perforin. No change in NK-cell expansion, conjugation with tumor target cells, or NK-cell expression of the pro-apoptotic protein granzyme B was observed. The serum component of the project is just now underway as we only recently received NASA IRB (Institutional Review Board) approval to request an additional blood sample from the Astronauts who participated in our 'Salivary Markers' flight study.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research has extensive Earth benefits. Using NASA funding, we have gained insight into many of the mechanisms governing NK-cell activity during spaceflight including CMV reactivation and stress. Many of the mechanisms of immunosuppression at play during spaceflight are also found on Earth particularly in the setting of solid organ or hematopoietic stem cell transplantation. CMV plays a major role in spaceflight-associated alterations to immune function and it also plays a major role in transplant outcome and cancer immunology. The findings that we have made through NASA and National Space Biomedical Research Institute (NSBRI) funding have led to two published first-author manuscripts during my NSBRI First Award Fellowship. These manuscripts focus on the beneficial effects of CMV on NK-cell-mediated cytotoxicity against hematologic malignancies and the mechanisms underpinning this anti-tumor effect. This research has resulted in an NIH R21 grant that will enable us to determine the effects of CMV seropositivity on multiple myeloma remission rates and also enable us to develop new ex vivo expansion protocols that selectively expand tumor-reactive NK-cells (like we see with CMV) for adoptive transfer without the negative side effects and decreased mortality associated with CMV reactivation in vivo.
Task Progress:	We have provided major insights into the mechanisms underpinning the impaired NK-cell-mediated immunity observed during spaceflight. Specifically, we have shown that simulated microgravity impairs NK-cell function similarly to spaceflight and identified the specific cellular adaptations responsible, thus enabling the development of countermeasures to help maintain immunity during exploration class missions. Our findings have contributed to closing gaps Immune (IM) IM1, IM2, and IM8. For IM1, we have shown that spaceflight inhibits NK-cell function and we have shown that this inhibition can be recapitulated using simulated microgravity as an analog. We have also identified the specific cellular adaptations responsible for the microgravity-induced inhibition of NK-cells. For IM2, we have shown that an improved immunological standard is necessary for spaceflight. Specifically, NK-cell function should be monitored as impaired NK-cell function has been linked to increased cancer risk. Maintaining NK-cell function will be particularly important for long-duration space exploration when astronauts are being exposed to high levels of cosmic radiation for long periods of time. For IM8, our serum stimulation experiment will allow us to mechanistically link stress (through hormones and cytokines present in serum) during spaceflight to impaired NK-cell function.
Bibliography Type:	Description: (Last Updated: 03/12/2021)
Articles in Peer-reviewed Journals	Bigley AB, Rezvani K, Shah N, Sekine T, Balneger N, Pistillo M, Agha N, Kunz H, O'Connor DP, Bollard CM, Simpson RJ. "Latent cytomegalovirus infection enhances anti-tumour cytotoxicity through accumulation of NKG2C+ NK cells in healthy humans." Clinical Experimental Immunology. 2016 Aug;185(2):239-51. https://doi.org/10.1111/cei.12785 ; PubMed PMID: 26940026; PubMed Central PMCID: PMC4955006 , Aug-2016
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