Fiscal Year:	FY 2017	**Task Last Updated:**	FY 01/26/2017
PI Name:	Cromer, Walter Ph.D.		
Project Title:	Fluid Shift Associated Lymphostasis of the Gut Induces Inflammation and Microbial Intolerance		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Human Factors and Performance Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Microhost**:Risk of Adverse Health Effects Due to Host-Microorganism Interactions		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	Flight,Ground	**Solicitation / Funding Source:**	2015 NSBRI-RFA-15-01 First Award Fellowships
Start Date:	10/01/2015	**End Date:**	10/01/2016
No. of Post Docs:	1	**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:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Zawieja, David Ph.D. (MENTOR/ Texas A&M University)		
Grant/Contract No.:	NCC 9-58-PF04308		
Performance Goal No.:			
Performance Goal Text:			

POSTDOCTORAL FELLOWSHIP
Original Aims: The original aims were to determine if there were inflammation in the intestines of rodents resulting from space flight, measure signs of lymphatic insufficiency in the intestine of space flown animals, examine lymphatic vessel/immune cell interaction in tissues of ground based analogs of microgravity, and determine if shifts in the microbiome of ground based microgravity analogs are analogous to those in space flight and check associated nutrition status.

Key Findings: We found evidence of inflammation in the intestines of rats flown for short duration (9 day), low Earth orbit (shuttle PARE 0.3) including edema and immune cell infiltration (via histopathology). This was supported by cytokine analysis that revealed that several key cytokine protein levels (IL-4, IL-5, IP-10, RANTES, etc.) were

Task Description:	up-regulated in the intestinal tissues of space flown animals and the profile suggests the initial phases of an inflammatory state. We also observed signs of lymphatic dysfunction with increased lipid droplet staining in the villi of the ileum and collapsed lymphatic vessels in the bowel wall of the colon that when considered together in the context of inflammation suggest a lymphatic functional deficiency. It is also likely that this dysfunction, at least in acute space flight, originates at the capillary lymphatic level given our observations of failed lipid uptake and collapsed pre-collecting lymphatic vessels with no other obvious signs of structural aberrations (no changes in perimeter of breaks in lymphatic endothelial staining). We were able to observe changes in the nature of lymphatic vessel/immune cell interactions in ground based models of microgravity in rats and mice (this is a critical regulator of lymphatic function) but not in space flown rats as the tissue was not available. We found that the number of MHCII positive antigen presenting cells (APCs) were decreased along mesenteric lymphatic collecting vessels in both mice and rats after 4 weeks of suspension. This was accompanied by a concomitant increase in number of potentially fibrotic CD146/CD206(int/low) macrophages along the vessels. We unfortunately were not able to test the antigen uptake and processing efficiency of the remaining APCs. We were able to perform limited micobiomic analysis of rat and mouse feces from simulated microgravity but have not yet received the comparison data for similar space flight animals. Our data suggests that rats in simulated microgravity have a shift in the microbiome similar to that of an animal fed a high fat diet with some aspect of immune suppression while similar samples from mice appear to resemble that from inflammatory bowel diseases. We were not able to complete nutritional analysis of the stools of space flown animals; however, lipid staining of the colon revealed that there was excessive lipid in the colon of space flown animals suggesting that fats are not being efficiently absorbed. Impact: Our data suggests that there is the very real possibility that aspects of space flight can interfere with lymphatic function in the visceral organs. While the effects are more pronounced in small rodent models (due to time and sensitivities) this is a factor that we need to be examining in human subjects as lymphatic function is critical to nutrition, wound healing, immune surveillance, and fluid balance. Proposed Research Plan: As this is a one year fellowship there are no current plans to expand upon this research with the National Space Biomedical Research Institute (NSBRI). However we have secured funding through NASA (myself as a Co-Investigator) to examine these factors (lymphatic dysfunction and inflammation) in animals flown for longer duration on the International Space Station (ISS). This will offer us a mechanism to fulfill several key parts of this project that we were not able to due to lack of appropriate tissue samples as well as extend our observations to longer time points.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This is a case where currently used ground based therapies for inflammatory bowel disease may be modified to meet the needs of the space flight community. Therefore this is accomplishing one of the goals that has been set for using currently available technologies developed on Earth in space flight capacities. These would potentially include testing of things like currently used probiotic treatments to reduce microbiome drift.
Task Progress:	We have achieved a majority of our goals proposed in the original grant. These include showing that there is impaired lymphatic transport from the intestine and inflammation in the bowels of space flown animals. We did have to substitute ground based analogs for space flown animals to show that there was reduced antigen presenting capacity along the lymphatic vessels themselves; however, we have recently come into possession of the tissues that we need for this. All currently achievable goals for this project have been completed as of October 2016 (project end date). Greater than 80% of the original specific aims have been completed and substitute aims have been implemented in place of goals that were not achievable due to issues of tissue access. We will be preparing manuscripts detailing our findings within the next month.
Bibliography Type:	Description: (Last Updated: 10/23/2024)
Articles in Peer-reviewed Journals	Cromer WE, Zawieja SD, Doersch KM, Stagg H, Hunter F, Tharakan B, Childs E, Zawieja DC. "Burn injury-associated MHCII(+) immune cell accumulation around lymphatic vessels of the mesentery and increased lymphatic endothelial permeability are blocked by doxycycline treatment." Lymphat Res Biol. 2018 Feb;16(1):56-64. Epub 2018 Jan 23. https://doi.org/10.1089/lrb.2017.0032 ; PubMed PMID: 29359999; PubMed Central PMCID: PMC5810432 , Feb-2018
Articles in Peer-reviewed Journals	Cromer WE, Zaweija DC. "Acute exposure to space flight results in evidence of reduced lymph transport, tissue fluid shifts, and immune alterations in the rat gastrointestinal system." Life Sci Space Res. 2018 May;17:74-82. https://doi.org/10.1016/j.lssr.2018.03.005 ; PubMed PMID: 29753416 , May-2018