Fiscal Year:	FY 2019	**Task Last Updated:**	FY 01/17/2019
PI Name:	Porada, Christopher Ph.D.		
Project Title:	Novel Microfluidic Biomarker Detection Platforms to Monitor In Vivo Effects of Solar Particle Events and Galactic Cosmic Rays Radiation, Using Mice with Human Hematopoietic Systems		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
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		
PI Email:	cporada@wakehealth.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	336-713-1655
Organization Name:	Wake Forest Institute for Regenerative Medicine		
PI Address 1:	391 Technology Way		
PI Address 2:			
PI Web Page:			
City:	Winston Salem	**State:**	NC
Zip Code:	27157	**Congressional District:**	5
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2017 HERO NNJ16ZSA001N-TRIRT. Appendix C: Translational Research Institute for Space Health (TRISH) Research Topics
Start Date:	11/01/2017	**End Date:**	10/31/2021
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	1	**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Almeida-Porada, Graca M.D., Ph.D. (Wake Forest Institute for Regenerative Medicine) Langefeld, Carl Ph.D. (Wake Forest School of Medicine) Walker, Stephen Ph.D. (Wake Forest Institute for Regenerative Medicine) Wilson, Paul Ph.D. (University of California, Davis) Coleman, Matthew Ph.D. (Wake Forest University) Zenhausern, Frederic Ph.D. (University of Arizona)		
Grant/Contract No.:	NNX16AO69A-T0103		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

We propose the following Specific Aims:
Aim 1: We will utilize mice with 'humanized' hematopoietic systems to define changes in human and mouse radiation/stress blood biomarkers in response to mission-relevant doses of simulated space radiation employing a microfluidic-based transcriptomic/proteomic biomarker detection platform; Aim 2: Validate the ability of nanoparticles (nanolipoproteins; NLPs) loaded with curcumin as effective countermeasures against the effects of simulated space radiation in both the human hematopoietic and mouse GI (gastroinstestinal) systems; Aim 3: Assess the suitability of curcumin-NLPs for use as radiation countermeasures in the space environment by: a) assessing their long-term stability for storage/use aboard the International Space Station (ISS) and long duration deep-space missions; b) evaluating their suitability for lyophilization/resuspension for oral delivery; and c) supplementing the diet of a small cohort of "humanized" mice with an optimized formulation to further evaluate their potential for both radioprotection (pre-irradiation supplementation) and radiation mitigation (post-irradiation supplementation). Aim 4: Use the innovative Human-Microbial Cross-Talk human 'gut-on-a-chip' model (HuMiX) to perform the first studies defining critical biomarker responses of mission-relevant doses of simulated space radiation on the human GI tract.

Approach: We will use 'humanized' immunodeficient (NSG) mice (huMice) whose hematopoietic system has been repopulated with human hematopoietic stem cells (HSC) from astronaut-age M/F donors. Using these huMice (3-4 months post-repopulation) as our experimental model, we will measure space radiation-induced human and mouse blood transcriptomic and proteomic changes using our low LET (linear energy transfer) photon-validated radiation biomarker detection panel and microfluidic-based detection platform. We will also test a promising curcumin-based nanolipoprotein (NLP)-based countermeasure that we have recently shown significantly improves human HSC proliferation and differentiation in vitro following low doses of high-energy proton and iron ions delivered at NASA Space Radiation Laboratory (NSRL). The huMice will serve as 'avatars' allowing us to study in vivo responses and leukemogenic potential of human hematopoietic systems exposed to modeled space radiation. HuMice will be developed and matured at Wake Forest Institute for Regenerative Medicine (WFIRM) and transported to Brookhaven National Laboratory (BNL), as will HuMiX 'gut-on-a-chip' populated with intestinal cells from healthy human donors (both sexes) of typical astronaut age. At NSRL, the huMice 'avatars' and HuMiX chips will be exposed to mission-relevant doses of high-energy protons, intermediate and high LET ions, and the GCR (galactic cosmic radiation) simulator. HuMiX chips will be monitored for short-term human GI cell biomarker responses, and the animals will be monitored for both short and long-term human and mouse biomarker responses, using our established low LET cesium-137 gamma radiation-specific protein biomarkers coupled to an ELISA-based microfluidic device that we will further optimize for ISS/in-flight use. Biomarker responses measured in these devices will be validated using qPCR, RNASeq, Western blotting, and several traditional and molecular radiobiological techniques. We will serially monitor animals for short and long term blood-based biomarker responses and physiological radiation effects (specifically leukemogenesis). We will submit tissue/organ samples of huMice to the NASA Human Research Program (HRP) Shared Tissue Repository, and our biomarker datasets will be deposited into the NASA GeneLab database.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

During future missions beyond low Earth orbit (LEO), such as those planned to Mars and near-Earth asteroids, astronauts will face poorly defined health risks as a result of exposure to space radiation in the form of solar energetic particles (SEP) consisting primarily of protons and light ions, and galactic cosmic rays (GCR) ranging from high-energy protons to high-energy charged (HZE) nuclei. Although the intensity of the GCR heavy ion flux is fairly low, the relative biological effectiveness (RBE) of these high charge and energy (HZE) particles can be extremely high. Long duration spaceflight can result in the accumulation of radiation exposures that may produce significant short- and long-term untoward effects on human physiology, and that could potentially increase cancer morbidity/mortality in astronauts. Unfortunately, an incomplete understanding of biological effects resulting from exposures to this unique/complex radiation environment and the paucity of human epidemiological studies for these radiation types make it difficult to accurately estimate risks of carcinogenesis for various organ sites due to exposure to space radiation. It is well appreciated that the stem cell compartments of the hematopoietic and gastrointestinal (GI) systems constitute some of the most radiosensitive tissues of the body. Leukemias represent one of the most frequent radiogenic cancers and also exhibit the shortest latency periods. Ionizing radiation is also an established risk factor for colorectal cancer, and the Fornace group demonstrated exposure to HZE ions significantly enhanced the development and progression of intestinal tumors in Adenomatous polyposis coli (APC) mouse models. Compounding the carcinogenic risks that could arise from low to intermediate dose SEP/GCR exposures are numerous studies collectively demonstrating that extended spaceflight conditions deleteriously affect the immune system at multiple levels and impair astronauts' ability to respond to infection or immune challenge. Collectively, these findings illustrate an important need to use appropriate human hematopoietic and GI experimental models to precisely identify SEP/GCR radiation-induced effects, namely to better understand the genomic and epigenomic alterations responsible for low or high LET charged particle-induced carcinogenesis; identify appropriate molecular targets for effective countermeasure development; and provide more refined datasets for NASA's risk estimation modeling effort.
Herein, we will perform studies in humanized mice to enable omics capability for in-flight measurements of radiation/stress blood biomarkers (human) using RNASeq and microfluidic-based transcriptomic/proteomic biomarker detection platforms. We will also utilize the highly innovative Human-Microbial Cross-Talk model (HuMiX) gut-on-a-chip to perform the first studies monitoring the effects of simulated space radiation on the human GI tract. Based on exciting preliminary data, we will also use RNASeq, the refined biomarker panels, and the HuMiX chip to examine the ability of the dietary supplement curcumin to prevent and/or mitigate the effects of space radiation on the hematopoietic and GI systems, and to determine the optimal working concentration for maximal radioprotective/radiomitigating effects. Given curcumin's poor water solubility, we will also perform studies to validate the ability of nanolipoprotein particles (NLP) loaded with curcumin (cNLPs) to serve as an effective countermeasure against the effects of SEP/GCR radiation in both the human hematopoietic and GI systems. We will also assess the stability of these cNLPs for long-term storage aboard ISS/long duration deep-space missions, suitability for lyophilization/resuspension for oral delivery, and as a potential radiomitigator post-exposure. If successful, these cNLPs could readily be implemented as a dietary supplement during prolonged missions, protecting astronauts from the deleterious effects space radiation exerts upon the hematopoietic and GI systems.

Task Progress:	The original Aims of this project were to: 1) use mice with "humanized" hematopoiesis to define changes in radiation/stress blood biomarkers in response to mission-relevant doses of simulated space radiation; 2) use the innovative Human-Microbial Cross-Talk human "gut-on-a-chip" model (HuMiX) to perform studies defining the effects of mission-relevant doses of simulated space radiation on the human GI tract; 3) validate the ability of nanolipoprotein particles (NLP) loaded with curcumin to serve as an effective countermeasure against the effects of simulated space radiation in both the human hematopoietic and GI models; and 4) assess the suitability of curcumin-NLPs as space radiation countermeasures. During the first partial year of funding, we have made significant progress towards achieving these goals. In the 8 months, we have: a) Performed H-plus 56Fe ion and gamma-ray irradiations on 84 wild-type mice, as requested by The Translational Research Institute for Space Health (TRISH), to provide in vivo comparator/validation of the in vitro HuMiX human gut-on-a-chip system; b) Collected tissues (at multiple times post-IR and are analyzing GI system, blood for biomarker identification by omics, and hematopoietic system for lineage alterations and DNA damage; c) Found marked histological alterations in small intestine in response to protons and iron ions; d) Discovered that exposure to Mars mission-relevant doses of protons and iron ions leads to disruption of the epithelial barrier of the small intestine, as assessed by immunofluorescent staining for Claudin-3; e) Humanized the hematopoietic system of the 1st cohort of 72 NSG mice and installed radio frequency identification (RFI)-tracking p-Chips for NSRL-18C; f) Optimized staining protocols for detecting human hematopoietic cells/lineages in humanized murine hosts; g) Miniaturized and optimized the HuMiX gut-on-a-chip platform to enable its use in the NSRL beamline; h) Performed pilot x-ray irradiations on HuMiX to validate this platform and optimize downstream analyses of radiation-induced molecular alterations and DNA damage; i) Successfully adapted HuMiX to enable use of primary human intestinal epithelial cells; j) Designed, formulated, and began testing curcumin-loaded NLPs for their ability to provide radioprotection in vivo in normal/wild-type mice; k) Showed cNLPs can mediate protection against SEP and GCR radiation in vivo, at omics level. Our progress to-date has provided us the technical tools we need to begin rigorously testing our hypotheses regarding the effects of space radiation (SEP and GCR) on the human hematopoietic and GI systems, and has provided preliminary evidence to support our hypothesis that a novel formulation of a readily available dietary supplement may have the ability to serve as an easy to administer countermeasure that can protect astronauts from at least some of the deleterious effects of space radiation during prolonged missions beyond LEO. Our omics work thus far has also begun to shed light on the molecular/biological pathways that are altered within multiple tissues as a result of exposure of a living organism to gamma-ray radiation and to simulated SEP and GCR radiation, and it is beginning to provide mechanistic clues regarding the means by which curcumin-NLPs mediate their protective effects.
Bibliography Type:	Description: (Last Updated: 07/01/2025)
Abstracts for Journals and Proceedings	Kuhlman B, Walker SJ, Langefeld C, Pardee T, Yang J, Lacombe J, Saxena M, Coleman MA, Zenhausern F, Almeida-Porada MG, Wilson PF, Porada CD. "Novel models to monitor in vivo effects of SPE/GCR radiation on human hematopoietic and GI systems." 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. , Sep-2018
Abstracts for Journals and Proceedings	Lacombe J, Yang J, Brooks C, Barret M, Duane B, Almeida-Porada G, Coleman MA, Wilson PF, Porada C, Zenhausern F. "Development of gut-on-chip to investigate in vivo effect of radiation." 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. , Sep-2018
Abstracts for Journals and Proceedings	Bicher S, He W, Evans AC, Shelby ML, Wilson PF, Kuhlman B, Porada CD, Almeida-Porada G, Schmid TE, Coleman MA. "Biologically inspired nanoparticles for radiation protection and mitigation." 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. 64th Annual Meeting of the Radiation Research Society, Chicago, IL, September 23-26, 2018. , Sep-2018
Abstracts for Journals and Proceedings	Kuhlman BM, Cordazzo Vargas B, Caudell D, Coleman MA, Almeida-Porada G, Wilson PF, Porada CD. "Defining the Effects of Mars Mission-Relevant Doses of SEP/GCR Radiation on the Small Intestine." 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. , Nov-2018
Abstracts for Journals and Proceedings	Kuhlman BM, Almeida-Porada G, Porada CD. "Microgravity Impairs Anti-Leukemic Activity of Human NK Cells." 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. , Nov-2018
Abstracts for Journals and Proceedings	Kuhlman B, Walker SJ, Langefeld C, Pardee T, Coleman MA, Zenhausern F, Almeida-Porada MG, Wilson PF, Porada CD. "Novel models to monitor in vivo effects of SPE/GCR radiation on human hematopoietic and GI systems." 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. 34th Annual Meeting of the American Society for Gravitational and Space Research, Bethesda, MD, October 31-November 3, 2018. , Nov-2018
Abstracts for Journals and Proceedings	Kuhlman BM, Almeida-Porada G, Porada CD. "Could Conditions of Microgravity Enhance Cancer Risk from Space Radiation?" 6th Annual NextGen Stem Cell Conference, Hartford, CT, August 2-3, 2018. 6th Annual NextGen Stem Cell Conference, Hartford, CT, August 2-3, 2018. , Aug-2018
Abstracts for Journals and Proceedings	Almeida-Porada MG, Walker SJ, Langefeld C, Pardee T, Kuhlman B, Coleman M, Zenhausern F, Wilson PF, Porada CD. "Novel microfluidic biomarker detection platforms to monitor effects of SPE and GCR radiation, using mice with human hematopoietic systems." 2018 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2018. 2018 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2018. , Jan-2018

Awards	Bicher S. (Sandra Bicher) "Top prize for posters in the Physical and Life Sciences category at the Annual Lawrence Livermore National Laboratory Student Poster Symposium, August 2018." Aug-2018