Fiscal Year:	FY 2022	**Task Last Updated:**	FY 03/19/2024
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		
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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:**	07/31/2022
No. of Post Docs:	0	**No. of PhD Degrees:**	1
No. of PhD Candidates:	3	**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:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/31/2022 per E. Urquieta/TRISH (Ed., 10/20/2021)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Zenhausern, Frederic Ph.D. (University of Arizona) Almeida-Porada, Graca M.D., Ph.D. (Wake Forest Institute for Regenerative Medicine) Walker, Stephen Ph.D. (Wake Forest Institute for Regenerative Medicine) Langefeld, Carl Ph.D. (Wake Forest Institute for Regenerative Medicine) Wilson, Paul Ph.D. (University of California, Davis) Coleman, Matthew Ph.D. (University of California, Davis) Tepper, Clifford Ph.D. (University of California, Davis) Lacombe, Jerome Ph.D. (University of Arizona) Yang, Jianing M.D., Ph.D. (University of Arizona)		
Grant/Contract No.:	NNX16AO69A-T0103		
Performance Goal No.:			

Performance Goal Text:	
Task Description:	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 gastrointestinal (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 International Space Station (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 (1 GeV/n 56Fe 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 efforts. Herein, we are performing 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 are also utilizing the Human-Microbial Cross-Talk model (HuMiX) gut-on-a-chip to perform the 1st studies monitoring the effects of simulated space radiation on the human GI tract. Based on exciting preliminary data, we will also 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 are also performing 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. Once validated as an effective countermeasure, we will also assess the stability of these cNLPs for long-term storage aboard ISS/long duration missions, suitability for lyophilization/resuspension for oral delivery. If successful, these cNLPs could readily be implemented as a dietary supplement during prolonged missions, protecting astronauts from the deleterious effects of space radiation on the hematopoietic and GI systems.
Task Progress:	The overall goal of the present project was to use novel in vivo humanized mice and a unique human gut-on-a-chip (HuMiX) platform to define the effects of Mars mission-equivalent does and species of SEP/GCR radiation on the human hematopoietic and GI systems, providing some of the first human data on these systems to aid with NASA’s risk estimates. Nearly 500 immunodeficient mice were repopulated with human hematopoietic stem cells (HSC) from astronaut-age M/F donors (huMice) to serve as “avatars” allowing us to study in vivo responses and leukemogenic potential of human hematopoietic systems exposed to modeled space radiation. At NSRL, human MRC-5 fibroblasts, the huMice “avatars”, and HuMiX chips were exposed to Mars mission-relevant doses of high-energy protons, intermediate and high LET ions (28Si, 16O, and 56Fe), and the 5-ion GCR simulator. In parallel, groups of each platform were used to test a promising curcumin nanolipoprotein (cNLP)-based countermeasure that we showed significantly improves human HSC proliferation and differentiation in vitro following low doses of high-energy proton and iron ions delivered at NSRL. Human fibroblasts were subjected to a battery of radiobiological assays, HuMiX chips were monitored for short-term human GI cell biomarker responses, and the huMice were monitored for both short and long-term biomarker responses, using our established low LET 137Cs-specific protein biomarkers coupled to an ELISA-based microfluidic device that was further optimized for ISS/in-flight use. Biomarker responses measured in these devices were validated using qPCR, RNASeq, Western blotting, and several traditional and molecular radiobiological techniques. We serially

	monitored animals for short- and long-term blood-based biomarker responses and physiological radiation effects (specifically leukemogenesis). The novel cNLP countermeasure was also lyophilized and used to prepare an orally available formulation that would be stable during prolonged spaceflight and awaits testing for efficacy.
Bibliography Type:	Description: (Last Updated: 07/01/2025)
Articles in Peer-reviewed Journals	Evans AC, Martin KA, Saxena M, Bicher S, Wheeler E, Cordova EJ, Porada CD, Almeida-Porada G, Kato TA, Wilson PF, Coleman MA. "Curcumin Nanodiscs Improve Solubility and Serve as Radiological Protectants against Ionizing Radiation Exposures in a Cell-Cycle Dependent Manner." Nanomaterials (Basel). 2022 Oct 15;12(20):3619. http://doi.org/10.3390/nano12203619 . PMID: 36296810 ; PMCID: PMC9609432 , Oct-2022
Awards	Kuhlman B. "Awarded Graduate Fellowship on National Institutes of Health (NIH) T32." Aug-2021
Awards	Diaz J. "Awarded Graduate Fellowship on National Institutes of Health (NIH) T32." Aug-2022