Fiscal Year:	FY 2022	**Task Last Updated:**	FY 08/18/2021
PI Name:	Cekanaviciute, Egle Ph.D.		
Project Title:	Astrocytes as Key Mediators of Central Nervous System Responses to Space Radiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H)		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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PI Organization Type:	NASA CENTER	**Phone:**	415-623-0033
Organization Name:	NASA Ames Research Center		
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Zip Code:	94035	**Congressional District:**	18
Comments:	NOTE: PI formerly at Universities Space Research Association at NASA Ames Research Center; became civil servant at NASA Ames in summer 2020.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2018 HERO 80JSC018N0001-Crew Health and Performance (FLAGSHIP, OMNIBUS). Appendix A-Flagship, Appendix B-Omnibus
Start Date:	10/17/2019	**End Date:**	09/30/2022
No. of Post Docs:		**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA ARC
Contact Monitor:	Whitmire, Alexandra	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 09/30/2022 per L. Juliette/JSC (Ed., 5/7/22) NOTE: End date changed to 12/31/2021 per information in PI report (Ed., 8/19/21) NOTE: End date changed to 9/30/2021 per F. Hernandez/ARC when PI became civil servant summer 2020 and project extended as internal project at NASA Ames; USRA grant 80NSSC20K0125 has official end date of 6/5/2020 (Ed., 9/2/2020)		
Key Personnel Changes/Previous PI:	NOTE (Ed., 9/2/2020): PI became civil servant at NASA Ames in summer 2020 ; project extended as internal project at NASA Ames and previous USRA grant 80NSSC20K0125 has official end date of 6/5/2020.		
COI Name (Institution):	Costes, Sylvain Ph.D. (NASA Ames Research Center)		
Grant/Contract No.:	Internal Project ; 80NSSC20K0125		
Performance Goal No.:			

Performance Goal Text:	
Task Description:	One of the main risks of human deep space exploration is central nervous system (CNS) damage, which is associated with neuronal damage and neuroinflammation, caused by exposure to space radiation combined with microgravity, and can lead to cognitive and behavioral dysfunction. CNS responses to injuries are strongly regulated by astrocytes, which are a major glial cell type in the brain that has also been shown to control the blood-brain barrier permeability, essential neuronal functions, and inflammation; and thus could serve as a robust CNS-specific target for countermeasure development. Therefore, we propose to investigate the astrocytic regulation of neuronal health in response to simulated space radiation. We propose to utilize for the first time a novel high-throughput human tissue-on-a-chip model for 3D neuronal/astrocyte cultures. We will investigate the morphological and physiological outcomes as well as gene expression changes after simulated space radiation exposure (5-ion simulation of galactic cosmic rays, 500 mGy) and compare them to the responses to gamma radiation in order to establish the relative biological effectiveness. We will also evaluate the necessity and sufficiency of astrocytes in regulating radiation responses by establishing experimental models where astrocytes are either the only cell type that is irradiated, or the only cell type that escapes irradiation. Finally, we will test whether driving astrocytes more towards A1 (inflammation) or towards A2 (scarring) phenotypes may serve as countermeasures by reducing radiation-mediated neuronal damage. In summary, we will examine whether astrocytes are necessary and sufficient to protect neurons from damage induced by simulated space radiation and evaluate their effectiveness as a target for further countermeasure development. We will also provide a proof of concept for human tissue-on-a-chip use for studying space radiation effects on the CNS. Our proposal addresses the Part "B. Basic Investigations Opportunity for Investigators New to NASA" of the Appendix B. The new investigator (Principal Investigator) and experienced investigator (CoInvestigator/Institutional Principal Investigator) have combined expertise in space biology, neuroinflammation astrocyte functions, TGFbeta functions in regulating astrocyte phenotypes, and responses to particle radiation. Thus, we have the capacity to complete this 1-year project at NASA Ames and, given sufficient interest, could easily expand it to a) investigate the outcomes of combined exposures to microgravity, stress, and radiation, and b) design an in vivo follow-up study on astrocytic regulation of CNS responses to spaceflight stressors.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	1. Technological. We have successfully developed human, 3D, multicellular, low footprint, high throughput (40-96 samples per standard 384-well plate) neurovascular model seeded with induced pluripotent stem cells (iPSC)-derived astrocytes and endothelial cells that retain blood-brain barrier properties and last for at least 1 week post irradiation and at least 2 weeks post seeding. This model could be used for personalized medicine approaches using iPSCs derived from specific individuals to test their responses to either therapeutic or space radiation. 2. Scientific. We have discovered that astrocytes are particularly sensitive to ionizing radiation, especially components of galactic cosmic rays. In response to radiation, astrocytes increase oxidative stress and blood-brain barrier permeability and cause immune dysregulation, at least in part via interleukin-1 signaling. These results are important not only for deep space exploration, but also for understanding the outcomes of human central nervous system irradiation for therapeutic purposes (e.g., to treat brain tumors), and results indicate astrocytic interleukin-1 signaling as a potential target for countermeasure/therapeutic development.
Task Progress:	1. ASTROCYTES EXACERBATE OXIDATIVE STRESS CAUSED BY SIMULATED DEEP SPACE RADIATION. We have further analyzed the neurovascular model responses to 600 MeV/n 56-Fe irradiation and observed a dose-dependent increase in oxidative stress. The presence of astrocytes exacerbated oxidative stress in irradiated models. Although oxidative stress induced by ionizing radiation, especially high-LET (linear energy transfer) particle radiation, has been extensively studied in CNS models, the relative susceptibility of astrocytes has not been evaluated previously. In combination with the role of astrocytes in exacerbating vascular permeability, this finding further indicates astrocytes as the “weakest link” in neurovascular responses to deep space radiation and a suitable target for countermeasures, and suggests oxidative stress as a key mechanism of radiation-induced damage. 2. ASTROCYTES EXACERBATE IMMUNE DYSFUNCTION CAUSED BY SIMULATED DEEP SPACE RADIATION. One of the main functions of astrocytes is regulating CNS immune responses in health and disease. Therefore, we used astrocyte and mixed endothelial cell-astrocyte neurovascular models to investigate the effects of simulated deep space radiation on astrocyte immunoregulatory characteristics. Secreted immune cytokines revealed a dysfunction in multiple pathways in astrocytes alone and in neurovascular models. Specifically, our results suggest that radiation disrupts astrocyte immunoregulatory functions, which exacerbates the effects of radiation on endothelial cell immune cytokine production, leading to neurovascular leakiness, increased inflammation and immune dysfunction. 3. ONGOING INVESTIGATIONS: NEUROVASCULAR RESPONSES TO 5-ION SIMPLIFIED SIMULATED GALACTIC COSMIC RAYS. Finally, during NASA Space Radiation Laboratory (NSRL) 21B campaign (June 2021), we exposed astrocyte-endothelial cell and astrocyte-neuron-endothelial cell combinations to 5-ion simplified simulated GCRs (SimGCRSim) and repeated 600 MeV/n 56Fe exposure to validate the results obtained during the previous irradiation experiment. Live imaging of neurovascular permeability was performed and samples were collected at different time points days post irradiation. Supernatants were frozen for oxidative stress and immune cytokine measurements, and neurovascular organ models were fixed and stained for immunohistochemistry. All sample analysis is ongoing.
Bibliography Type:	Description: (Last Updated: 06/23/2023)
Articles in Peer-reviewed Journals	Afshinnekoo E, Scott RT, MacKay MJ, Pariset E, Cekanaviciute E, Barker R, Gilroy S, Hassane D, Smith SM, Zwart SR, Nelman-Gonzalez M, Crucian BE, Ponomarev SA, Orlov OI, Shiba D, Muratani M, Yamamoto M, Richards SE, Vaishampayan PA, Meydan C, Foox J, Myrrhe J, Istasse E, Singh N, Venkateswaran K, Keune JA, Ray HE, Basner M, Miller J, Vitaterna MH, Taylor DM, Wallace D, Rubins K, Bailey SM, Grabham P, Costes SV, Mason CE, Beheshti A. "Fundamental biological features of spaceflight: Advancing the field to enable deep-space exploration." Cell. 2020 Nov 25;183(5):1162-84. Review. https://doi.org/10.1016/j.cell.2020.10.050 ; PMID: 33242416 , Nov-2020

Awards	Cekanaviciute E. "Early Career Investigator Spotlight, Radiation Research Society, March 2021. " Mar-2021