Fiscal Year:	FY 2020	**Task Last Updated:**	FY 03/13/2020
PI Name:	Wyrobek, Andrew Ph.D.		
Project Title:	Variation in CNS Damage Signaling and Blood Sentinels of Neuropathology After Exposure 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 (2) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	For immediate assistance please contact my administrator Caron LaMarsh clamarsh@lbl.gov, 510.486.5317		
Project Type:	GROUND	**Solicitation / Funding Source:**	2017 HERO 80JSC017N0001-Crew Health and Performance (FLAGSHIP1, OMNIBUS). Appendix A-Flagship1, Appendix B-Omnibus
Start Date:	04/01/2019	**End Date:**	12/31/2021
No. of Post Docs:	4	**No. of PhD Degrees:**	0
No. of PhD Candidates:	3	**No. of Master' Degrees:**	0
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NASA JSC
Contact Monitor:	Williams, Thomas	**Contact Phone:**	281-483-8773
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/31/2021 per D. Kulkarni/HRP (Ed., 10/7/21) NOTE: Period of performance changed to 4/1/2019-3/31/2021 per PI/NASA-LBL interagency agreement; previous information showed 11/28/18-11/27/20 (Ed., 9/5/19)		
Key Personnel Changes/Previous PI:	March 2020 report: The individuals are co-investigators on this project: Peterson, Leif; Bowles, Dawn; Celniker, Susan; Witkowska, Helena. The following individuals remain as collaborators on this project: Albou, Laurent-Philippe; Mungall, Chris; Fiehn, Oliver; Settles, Matthew; Froenicke, Lutz; Straume, Tore.		
COI Name (Institution):	Peterson, Leif Ph.D. (The Methodist Hospital Research Institute) Bowles, Dawn Ph.D. (Duke University) Celniker, Susan Ph.D. (Lawrence Berkeley National Laboratory) Witkowska, Helena Ph.D. (University of California San Francisco - ret)		
Grant/Contract No.:	80JSC019T0007		
Performance Goal No.:			

Performance Goal Text:	
Task Description:	Major objectives of the NASA space radiation research program are to enable human exploration of space without exceeding limits for immediate and persistent risks to the central nervous system (CNS) from space radiation. The proposed research will investigate the CNS subregions of rodents exposed to simulated space radiation for molecular indicators for vascular damage, inflammation, and neurological abnormalities after space radiation. This project will apply multi-omic technologies (proteomics, metabolomics, and bioinformatics) to archived CNS brain subregions from irradiated mouse and rat behavioral models. The specific aims are: Aim 1. Characterize the persistence of radiation-induced molecular abnormalities in cortex and hippocampus after low-dose exposures to 56Fe particles, and compare the predictions for CNS tissue damage and late-onset neuropathologies in similarly irradiated mice and rats. Aim 2. Identify persistent bio-effect markers in peripheral blood and cerebrospinal fluid (CSF) that correlate with molecular damage in CNS vascular or immune functions. Our research plan will provide testable hypotheses of CNS tissue damage and identify molecular targets for susceptible pathways/functions of CNS damage. This project will also provide proof-of-principle whether CNS damage relevant bio-effect metabolites can be detected in CSF and blood. This project will also identify radiation-sensitive pathways, suitable for future development of biological countermeasures to reduce CNS risks from space radiation. The results of this research are designed to help NASA reduce the uncertainty associated with during mission behavior and CNS risk for astronauts on deep space exploration missions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The predictive model developed in this project will yield numerous hypotheses of mechanisms of CNS radiation damage that are either common or unique to cortex and hippocampus – these hypotheses will be tested in future studies by in situ analyses of archived frozen tissues and fixed contralateral hemispheres that are available from all animals in this proposal. This project will also provide proof-of-principle whether CNS damage relevant bio-effect metabolites can be detected in CSF and blood. This project will also identify radiation-sensitive pathways, suitable for future development of biological countermeasures to reduce CNS risks from space radiation. The results of this research are designed to help NASA reduce the uncertainty associated with during mission behavior and CNS risk for astronauts on deep space exploration missions.
Task Progress:	This new project will provide NASA with a deeper understanding of the cellular and molecular mechanisms underlying persistent CNS tissue abnormalities and the risks for late-onset neuropathology after exposures to space radiation. This project uses archived tissues from “middle-aged” male rats and mice exposed to space-relevant fluences of 56Fe particle radiation to investigate the persistence of CNS molecular damage across two rodent species and to assess the relevance to astronauts for behavioral deficits during deep-space missions and for neurological risks after return to Earth. Our research plan is to develop a predictive model of the mechanisms of CNS damage and risks for neuropathology. We propose to build this model using high-complexity, multi-omic measurements (proteomics, untargeted metabolomics, complex lipid metabolomics, and 3’TAGseq transcriptomics) in the cortex and hippocampus within animals for which we have blood in all cases and CSF in many. The predictions of the model for CNS damage and neuropathologies will be linked to molecular changes that can be measured in biofluids, and can be verified in situ in archived tissues. The specific aims are: Aim 1. Characterize the persistence of radiation-induced molecular abnormalities in cortex and hippocampus after low-dose exposures to 56Fe particles, and compare the predictions for CNS tissue damage and late-onset neuro-pathologies in similarly irradiated mice and rats. Aim1A will use archived CNS tissue from Sprague Dawley (SD) rats collected at 4 and 9 months after low-dose exposures, and generate new transcriptomics (3’TAGseq) and new metabolomics profiles (untargeted metabolism and targeted complex lipids) from cortex and hippocampus. These data will be integrated with prior proteomics profiles from hippocampus at 9 months after exposure to build a predictive model of CNS tissue damage and risks for neuropathology, with emphasis on vascular and immune abnormalities. Aim1B will compare molecular responses in cortex and hippocampus of mice and rats at 9 months after exposure to evaluate cross-species consistency. The predictive model will be built using integrating bioinformatics and biostatistical approaches. Aim 2. Identify persistent bio-effect markers in peripheral blood and CSF that correlate with molecular damage in CNS vascular or immune functions. Aim2A will apply targeted metabolite profiling to search in rat CSF and peripheral blood plasma of the 4-month cohort for metabolites that were found in Aim1 to be associated with CNS vascular and immune abnormalities cortex and hippocampus. Aim2B will investigate selected CSF and plasma bio-effects markers of CNS vascular and immune dysfunction in rats that were characterized for high and low anxiety performance on Elevated Plus Maze after exposure. The predictive model developed in this project will yield numerous hypotheses of mechanisms of CNS radiation damage that are either common or unique to cortex and hippocampus – these hypotheses will be tested in future studies by in situ analyses of archived frozen tissues and fixed contralateral hemispheres that are available from all animals in this proposal. This project will also provide proof-of-principle whether CNS damage relevant bio-effect metabolites can be detected in CSF and blood. This project will also identify radiation-sensitive pathways, suitable for future development of biological countermeasures to reduce CNS risks from space radiation. The results of this research are designed to help NASA reduce the uncertainty associated with during mission behavior and CNS risk for astronauts on deep space exploration missions.
Bibliography Type:	Description: (Last Updated: 02/08/2018)