Fiscal Year:	FY 2020	**Task Last Updated:**	FY 11/24/2020
PI Name:	Kiffer, Frederico C. Ph.D.		
Project Title:	Effects of Galactic Cosmic Radiation on Translationally-Relevant Cognitive Behaviors and Response to Social Stress		
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:	fredkiffer@gmail.com	**Fax:**	FY
PI Organization Type:	NON-PROFIT	**Phone:**	831-419-2676
Organization Name:	Children's Hospital of Philadelphia		
PI Address 1:	3615 Civic Center Blvd		
PI Address 2:	Room 402 F Abramson Pediatric Research Center		
PI Web Page:			
City:	Philadelphia	**State:**	PA
Zip Code:	19104-4318	**Congressional District:**	3
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2019 TRISH RFA-1901-PD Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
Start Date:	08/01/2019	**End Date:**	07/31/2022
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:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/31/2022 per E. Urquieta/TRISH (Ed., 7/1/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Eisch, Amelia Ph.D. (Mentor: Children's Hospital of Philadelphia)		
Grant/Contract No.:	NNX16AO69A-P0402		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Astronauts on a Mars mission will be exposed to potentially harmful levels of charged-particle radiation. Thirty years of basic research with ground-based charged-particle radiation has provided overwhelming evidence that the rodent Central Nervous System (CNS) and behavior are negatively affected by charged-particles, suggesting this is a concern for astronaut health. However, the current literature has several caveats, including using young rather than fully-adult rodents, lack of studies focused on the female rodent CNS, unrealistic single-particle radiation simulations, lack of feasible therapeutic countermeasures, and behavioral tests with low translational potential and high handling- or experimenter-induced variability. Additionally, no published CNS study has yet assessed the effects of charged-particle radiation in combination with spaceflight-relevant stressors. We will address these limitations by exposing male and female mice of astronaut age to a novel, complex, but realistic Galactic Cosmic Ray simulation (GCR) and then examining network-dependent behavioral performance on a highly-translational, appetitive touch-screen platform, including a behavioral test battery that can be viewed as analogous to the tests currently used on astronauts aboard the International Space Station. A separate group of mice will be examined for the influence of GCR on their ability to cope with social and physical stress in a validated mouse model of depression. Finally, we will test a promising anti-inflammatory drug, its ability to prevent GCR-induced deficits in cognition and social defeat stress. This proposal will address a wide range of NASA-defined knowledge gaps in its Human Research Roadmap. Specifically, we strive to provide a model basis for identifying individuals who are resilient to the extreme spaceflight conditions, validate a measure for monitoring behavioral health, determine radiation dose thresholds for behavioral measures in a domain basis and in combination with social defeat stress, all of which will help inform NASA's risk models for a crewed mission to Mars.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our preliminary data, which result from one of the first rodent exposures to the NASA Space Radiation Laboratory (NSRL)'s acute 33-beam Galactic Cosmic Ray (GCR), suggest that the mission-relevant dose of 750 mGy does not result in the same behavioral deficits commonly reported in the monoenergetic single- or simple ion combination literature for aged mice. However, we still observed radiation-induced deficits following radiation exposure. We show that this novel radiation paradigm carries cognitive behavioral risk in mice, suggesting the possibility that the same may be true in human exposures. We also demonstrate radio-protective properties of CDDO-EA and evaluate its use as a candidate radiation countermeasure. CDDO-EA prevented numerous radiation-related deficits in females, but did not appear to be an effective countermeasure in males.
Task Progress:	1.Original Project Aims/Objectives Astronauts on a Mars mission will be exposed to potentially harmful levels of charged-particle radiation. Thirty years of basic research with ground-based charged-particle radiation has provided overwhelming evidence that the rodent Central Nervous System (CNS) and behavior are negatively affected by charged-particles, suggesting this is a concern for astronaut health. However, the current literature has several caveats, including using young rather than fully-adult rodents, lack of studies focused on the female rodent CNS, unrealistic single-particle radiation simulations, lack of feasible therapeutic countermeasures, and behavioral tests with low translational potential and high handling- or experimenter-induced variability. Additionally, no published CNS study has yet assessed the effects of charged-particle radiation in combination with spaceflight-relevant stressors. We will address these limitations by exposing male and female mice of astronaut age to a novel, complex, but realistic Galactic Cosmic Ray simulation (GCR) and then examining network-dependent behavioral performance on a highly-translational, appetitive touch-screen platform, including a behavioral test battery that can be viewed as analogous to the tests currently used on astronauts aboard the International Space Station (ISS). A separate group of mice will be examined for the influence of GCR on their ability to cope with social and physical stress in a validated mouse model of depression. Finally, we will test a promising anti-inflammatory drug for its ability to prevent GCR-induced deficits in cognition and social defeat stress. This proposal will address a wide range of NASA-defined knowledge gaps in its Human Research Roadmap. Specifically, we strive to provide a model basis for identifying individuals who are resilient to the extreme spaceflight conditions, validate a measure for monitoring behavioral health, determine radiation dose thresholds for behavioral measures in a domain basis and in combination with social defeat stress, all of which will help inform NASA's risk models for a crewed mission to Mars. We are working to achieve these goals by fulfilling gaps in knowledge addressed in our specific aims: Aim 1. Define GCR effects on translationally-relevant cognitive tests in mice. Aim 2. Define the outcomes of GCR on adaptive, social-stress-mediated behavior. 2. Key Findings We have exposed 6-month-old male and female mice to an acute 750 mGy dose of the NSRL's 33-beam GCR simulation (NSRL 19A, collaboration with Jerry Shay, University of Texas Southwestern). 4 months following exposure, we tested males for open field activity, anxious behavior via the elevated-plus maze, object memory via the Novel Object Recognition test, and sociability and social recognition by the 3-Chamber Social Interaction test. Female mice were trained and tested on an appetitive touchscreen platform for an object-based location discrimination task, a simple, rule-based operant acquisition test, and an extinction learning test. Following touchscreen-based testing, females were subsequently tested on the same behavioral tasks as the male mice, with additional marble burying, and nestlet digging tests. We are currently processing and validating these behavioral data targeted at fulfilling Aim 1. 3. Proposed Research Plan for the Coming Year Our Aim 2 approach was initially to define the outcomes of GCR on adaptive, social-stress-mediated behavior using the social defeat-stress model. Due to the COVID-19 pandemic lab shut-down and limitations on animal case staff, we were unable to maintain our colony of mice needed to perform social defeat stress (e.g., screened CD-1 retired breeders which we used as aggressors). While the labs re-opened in June to 25% capacity as long as personnel were masked and at least 6-feet apart, we still were unable to perform social defeat stress since a) it would take ~2month to re-order and screen aggressors, at which point the experimental mice may be too old to use for social defeat; and b) we are unable to

	perform the screening and the subsequent social defeat stress with the personnel restrictions in place. Therefore, we did research to assess an alternative behavioral model in which to define the outcomes of GCR on adaptive, social-stress-mediated behavior. After intense consideration, we pivoted to the tube dominance test for social hierarchy, a test that also involves social stress as an experimental condition. We are currently conducting behavioral experiments including the tube dominance test in male and female mice that during NSRL 19C received 3 x 67 mGy fractions of 56Fe (600 MeV/n) over the course of 5 days. The resulting data will help address how prior 56Fe exposure (a significant dose-contributing component of GCR) at 6 months of age influences social-stress-mediated behavior 9 months later. We are also preparing a future experiment assessing the effects of a chronic proton exposure equivalent to the NSRL GCR simulation on hippocampal neurogenesis.
Bibliography Type:	Description: (Last Updated: 08/21/2023)
Articles in Peer-reviewed Journals	Kiffer F, Alexander T, Anderson J, Groves T, McElroy T, Wang J, Sridharan V, Bauer M, Boerma M, Allen A. "Late effects of 1H + 16O on short-term and object memory, hippocampal dendritic morphology and mutagenesis." Front Behav Neurosci. 2020 Jun 26;14:96. https://doi.org/10.3389/fnbeh.2020.00096 ; PMID: 32670032 ; PMCID: PMC7332779 , Jun-2020
Awards	Kiffer F. "Outstanding Paper Award for Young Scientists, 43rd Committee on Space Research (COSPAR) Scientific Assembly--Hybrid, to be held January 2021." Jan-2021
Awards	Kiffer F. "Radiation Research Society Scholar in Training Committee Election, November 2019." Nov-2019