Fiscal Year:	FY 2020	**Task Last Updated:**	FY 12/03/2019
PI Name:	Azzam, Edouard Ph.D.		
Project Title:	Oxidative Stress and the Cancer Risk of Space Radiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	Newark	**State:**	NJ
Zip Code:	07103	**Congressional District:**	10
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-RADIATION
Start Date:	01/15/2015	**End Date:**	07/14/2021
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: Extended to 7/14/2021 per NSSC information (Ed., 4/28/21) NOTE: Extended to 1/14/2021 per NSSC information (Ed., 2/11/2020) NOTE: Extended to 1/14/2020 per NSSC information (Ed., 3/12/19)		
Key Personnel Changes/Previous PI:	NOTE: Principal Investigator Edouard Azzam, Ph.D., retired in early 2021 and CoI Roger Howell, Ph.D., was named PI for university admin purposes only. Dr. Azzam remains as principal researcher.		
COI Name (Institution):	de Toledo, Sonia Ph.D. (Rutgers University, New Jersey Medical School) Howell, Roger Ph.D. (Rutgers University, New Jersey Medical School) Pain, Debkumar Ph.D. (Rutgers University, New Jersey Medical School)		
Grant/Contract No.:	NNX15AD62G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The objective of this project is to investigate transient and persistent oxidative stress, and its association with cancer induction, after exposure of mice to low doses/fluences of different types of space radiation. The proposal is based on the hypothesis that space radiations with different biophysical properties induce distinct redox-modulated biochemical changes. Such changes may differentially perturb physiological functions and may induce DNA damage to different extents. If they persist, some of these changes may lead to cancer. This is an immediate concern to NASA, particularly in the context of long-duration exploratory space missions. This proposal will use middle-aged mice to determine the effects of space radiation on critical redox-modulated cellular processes. Experiments will include exposures to low doses of different high energy particles (oxygen, calcium, and silicon), delivered at low dose-rate. The results will be compared with those obtained in mice exposed in parallel to cesium-137 gamma rays. We will examine acute and chronic oxidative changes in DNA, and in lipids and proteins involved in critical signaling pathways that mediate the cellular responses to stress. We will measure these changes in radiation sensitive and resistant organs following whole or partial body irradiation of mice strains that vary in their susceptibility to cancer. We will also investigate stressful effects in irradiated organs/tissues and their propagation to non-irradiated organs/tissues. We will explore the possibility that prior exposure to high energy protons induces mechanisms that protect tissues from the targeted and non-targeted stresses due to a subsequent exposure to low fluences of highly damaging energetic particles. The goal is to generate data related to Specific Gaps in knowledge listed in Cancer 1-Cancer 5 and in Cancer-7, which may help reduce the uncertainty in estimating cancer risk to astronauts.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	There is overwhelming evidence to support that oxidative stress contributes to elevated levels of DNA damage, abnormal growth control, and altered metabolic pathways, which can lead to cancer. However, the effects of space ionizing radiation (IR) on these processes in vivo and the underlying signaling events have not been identified, particularly in the context of chronic exposure to low fluences of energetic high atomic number and high energy (HZE) particles that vary in their linear energy transfer (LET). The issue is further complicated by the fact that astronauts are exposed to mixed types of IR. An exposure to a low dose of low-LET IR prior to a dose from high-LET IR may induce protective processes that attenuate the damaging effects of the latter. This is important because the low flux of the high-LET HZE radiations in space relative to the higher flux of low-LET protons makes it highly probable that for any given cell in the body, proton events will precede any HZE event. Assessing these targeted and non- targeted responses will synergize with other NASA supported studies and will contribute crucial and novel mechanistic information to ongoing efforts in developing biophysical models for predicting health risks to astronauts. By achieving an integrated understanding of the endpoints investigated in this proposal, a rational path towards preventing the occurrence or delaying the onset of cancer (and other adverse health effects) during or after space missions may be developed. Further, as particle therapy is being increasingly used to treat cancer, the proposed studies may lead to the development of treatment protocols that enhance the efficacy of anti-tumor treatments and attenuate post therapeutic out-of-field normal tissue toxicity.
Task Progress:	Progress in accomplishing the research outlined in our investigation of oxidative stress and the cancer risk of space radiation continues to occur. Pathological examination of structural and neoplastic changes in tissues of male CBA/CaJ that were sacrificed at different times after exposure to various types of space radiation, including protons and energetic heavy particles is proceeding and the results are being analyzed. The experimental approach was, briefly, as follows: middle-aged CBA/CaJ mice (9-10 month old) were exposed (whole or partial body) to energetic protons, calcium (Ca), silicon (Si), or oxygen (O) ions with an isovelocity of 1 GeV/nucleon, and respective average Linear Energy Transfer (LET) values of ~0.24, 14, 44, and 88 keV/µm. A different set of mice was exposed to gamma rays from a cesium-137 source as reference radiation (LET ~ 0.9 keV/µm). The dose received from the energetic protons was 20 cGy delivered over 1 hour. The mice exposed to Ca ions received a dose of either 20, 30, or 40 cGy. Those exposed to the Si or O ions received 40 cGy. The total doses of radiation from these heavy particles (i.e., Ca, Si, O ions) were delivered either as single acute bolus, or in 3 fractions (1 acute fraction/day over 3 days). In previous reports, we described our findings on the effects of space radiation on the abundance of hematopoietic cells and the bone marrow microenvironment. We also reported on tissue injury in liver and lung, and on the effects on bone density and cardiac function. During the past year, we expanded our investigation of tissue injury and analyzed oxidative stress in kidney. We also expanded our analyses of cardiac function and bone. Kidney: Using in situ immunodetection and immunoblotting techniques, we found that the kidneys of mice exposed to energetic calcium ions 15 months earlier harbored increased levels of proteins with lipid peroxide adducts, which is suggestive of persistent inflammatory responses. These increases were highly significant when the mice were exposed to 40 cGy of Ca ions delivered either as a single bolus or in a fractionated manner. At 2 weeks after irradiation, no significant changes in lipid peroxidation were detected. Heart: In the hearts of mice exposed to either energetic calcium ions or gamma rays, similarity in blood ejection fraction and pulmonary artery/aorta diameter ratio suggests that the left and right side's heart functions are equivalent within groups without any sign of heart failure. However, the left ventricle (LV) dimension, volume, and output parameter showed a tendency in LV size reduction, especially in the Calcium 40 cGy (fractionated) group. Ongoing analyses are being extended to examine fibrosis in both the right and left ventricles and in the tricuspid valve, whether a possible relation with right atrium and liver enlargement exists. The mice exposed to fractionated dose of 40 cGy from energetic oxygen or silicon ions did not show significant difference within the groups. The only significant difference is in the change in fractional area where the control group exhibited higher fractional area than the silicon and gamma-irradiated groups. Bone: Ongoing analyses of computed tomography scans of the skeletons of the mice exposed to the various types of space radiation are using artificial intelligence to gauge qualitative and quantitative changes at 15 months after irradiation.
Bibliography Type:	Description: (Last Updated: 04/05/2023)

Abstracts for Journals and Proceedings	Herbig LS, Moore L, Chidambaram S, da Silva A, Herbig U, Azzam EI. "Cosmic radiation does not cause persistent telomeric double stranded breaks in mouse brain." Presented at 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. Abstracts. 2019 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 22-25, 2019. , Jan-2019
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Articles in Peer-reviewed Journals	Colangelo NW, Azzam EI. "The importance and clinical implications of flash ultra-high dose-rate studies for proton and heavy ion radiotherapy." Radiation Research 2020 Jan;93(1):1-4. https://doi.org/10.1667/RR15537.1 ; PMID: 31657670; PMCID: PMC6949397 , Jan-2020