Fiscal Year:	FY 2016	**Task Last Updated:**	FY 01/13/2016
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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Zip Code:	07103	**Congressional District:**	10
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-RADIATION
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No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
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)		
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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:	The radiation studies outlined in the project have been initiated during Run 15C at the NASA Space Radiation Laboratory (NSRL) in November 2015. In studies related to the three Specific Aims, groups of middle-aged CBA/CaJ mice were exposed (whole or partial body) to either 1 GeV protons, 1 GeV/u Ca ions, or cesium-137 gamma rays to examine the following: 1- Chronic oxidative stresses and inflammatory responses in organs that differ in their radiation sensitivity 2- To evaluate the relative biological effectiveness of 1 GeV/u Ca ions compared to acute 137Cs gamma rays in enhancing the rate of cancer incidence 3- To determine the beneficial effects of a pre-exposure to low linear energy transfer (LET) protons that may minimize the harmful effects (oxidative stress, DNA damage) of a subsequent exposure to high LET Ca ions 4- To measure oxidative changes and cancer incidence in non-irradiated organs (liver, lung) after exposure of the head to an acute mean absorbed dose of 0.4 Gy of 1 GeV/u Ca, and to compare the observed changes with those in the targeted organ (brain) 5- To examine the protective effect of whole-body pre-exposure to a conditioning dose of 0.2 Gy of 1 GeV protons delivered at low dose-rate prior to head exposure to acute dose of 0.4 Gy of 1 GeV/u Ca ions At two weeks after exposure, 5 mice from each of the groups described below were sacrificed, and peripheral blood as well as different organs (heart, liver, lung, kidney, bone marrow, and brain) were harvested for cellular, biochemical, molecular, and histological analyses. The groups of mice were as follows: 1: Control ; 2: Gamma rays: 1.5 Gy (acute, single fraction, whole body); 3: Gamma rays: 3 Gy (acute, single fraction, whole body); 4: 1 GeV protons: 0.2 Gy (0.0035 Gy/min, whole body); 5: 1 GeV/u Ca: 0.2 Gy (in 3 fractions; 1 acute fraction/day; whole body); 6: 1 GeV/u Ca: 0.3 Gy (in 3 fractions; 1 acute fraction/day; whole body); 7: 1 GeV/u Ca: 0.4 Gy (in 3 fractions; 1 acute fraction/day; whole body); 8: 1 GeV/u Ca: 0.4 Gy (in 1 acute fraction; whole body); 9: 1 GeV/u Ca: 0.4 Gy (in 1 acute single fraction delivered to the head only); 10: 1 GeV protons followed by 1 GeV/u Ca: whole body exposure to 0.2 Gy of protons delivered 24 h prior to 0.4 Gy of 1 GeV/u Ca ions delivered to the whole body; 11: 1 GeV protons followed by 1 GeV/u Ca: whole body exposure to 0.2 Gy of protons delivered 24 h prior to 0.4 Gy of 1 GeV/u Ca ions targeted to the head only. PRELIMINARY RESULTS: Assays analyzing the effects of the different radiation delivery regimens described above on inflammatory cytokines, changes in abundance of immune cells, as well as redox modulated changes affecting the activity of enzymes implicated in oxidative metabolism are ongoing. Inflammatory Cytokines: Preliminary analyses of a panel of inflammatory cytokines revealed prominent changes in the levels of several cytokines in blood plasma. The results strongly support a modulatory effects on the immune system and inflammatory responses by energetic calcium ions. Blood Cells: Analysis of lymphoid (T, B, and NK sub-populations) and myeloid (monocytes/macrophages and neutrophils) cells in peripheral blood was performed. Among many alterations in abundance of cellular subsets, prominent changes were observed in the abundance of neutrophils and CD4+ T-helper lymphocytes, which are an

	essential part of the immune system. Notably, the changes reflect a significant modulating effect of fractionation of the radiation dose from calcium ions. Biochemical Changes: Preliminary analyses of a battery of enzymes suggest that mitochondria, the major contributor to oxidative metabolism, may be particularly susceptible to space radiation-induced damage. In particular, mitochondrial Lon, an ATP-powered proteolytic machine that selectively degrades key rate limiting proteins as well as misfolded, unassembled, and oxidatively damaged proteins, is sensitively regulated by space radiation.
Bibliography Type:	Description: (Last Updated: 04/05/2023)
Articles in Peer-reviewed Journals	Nicolas F, Wu C, Bukhari S, de Toledo SM, Li H, Shibata M, Azzam EI. "S-nitrosylation in organs of mice exposed to low or high doses of gamma-rays: The modulating effect of iodine contrast agent at a low radiation dose." Proteomes. 2015 Apr 28;3(2):56-73. http://dx.doi.org/10.3390/proteomes3020056 ; PubMed PMID: 26317069; PubMed Central PMCID: PMC4548934 , Apr-2015
Articles in Peer-reviewed Journals	Azzam EI, Colangelo N, Domogauer JD, Sharma N, de Toledo SM. "Is ionizing radiation harmful at any exposure? an echo that continues to vibrate." Health Phys. 2016 Mar;110(3):249-51. http://dx.doi.org/10.1097/HP.0000000000000450 ; PubMed PMID: 26808874; PubMed Central PMCID: PMC4729313 , Mar-2016
Articles in Peer-reviewed Journals	Chen H, Goodus MT, de Toledo SM, Azzam EI, Levison SW, Souayah N. "Ionizing radiation perturbs cell cycle progression of neural precursors in the subventricular zone without affecting their long-term self-renewal." ASN Neuro. 2015 Jun 8;7(3). Print 2015 May-Jun. http://dx.doi.org/10.1177/1759091415578026 ; PubMed PMID: 26056396; PubMed Central PMCID: PMC4461572 , Jun-2015