Fiscal Year:	FY 2021	**Task Last Updated:**	FY 11/24/2020
PI Name:	Pariset, Eloise Ph.D.		
Project Title:	Investigation of Blood-based Circulating Biomarkers of Responses to Space Radiation (Postdoctoral Fellowship)		
Division Name:	Human Research		
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Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
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Human Research Program Risks:	None		
Space Biology Element:	None		
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Zip Code:	94035-0001	**Congressional District:**	18
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Project Type:	GROUND	**Solicitation / Funding Source:**	2019 TRISH RFA-1901-PD Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
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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:			
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Flight Assignment:	NOTE: End date changed to 1/31/2022 (originally 10/31/2021) per TRISH (Ed., 6/1/2020)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Costes, Sylvain Ph.D. (Mentor: NASA Ames Research Center)		
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Task Description:	POSTDOCTORAL FELLOWSHIP Understanding the mechanisms underlying the human responses to space radiation is a high priority for upcoming lunar and Mars missions and could enable preventive actions and countermeasures to avoid radiation-induced risks. Peripheral blood lymphocytes have been commonly studied to evaluate radiation-induced biological responses since they are easily accessible, can provide individual assessment of radiation sensitivity, and are among the most radiosensitive cell types in the human body. Our laboratory aims at understanding the individual variability of human sensitivity to ionizing radiation, for the first time focusing on space-relevant high mass and charge (HZE) particle radiation based on DNA and cellular damage in Peripheral Blood Mononuclear Cells (PBMCs) and genomic associations. Here we propose to extend this ongoing study by identifying blood-based circulating factors regulating radiation responses in humans, which will provide better understanding of how radiation influences human health to develop countermeasures. We will study radiation-induced damage in human immune cells following exposure to two types of space-relevant radiation (gamma ray and Fe particles), with a focus on expression changes and functional roles of two types of blood-based biomarkers: cytokines (small proteins) and exosomes (extracellular vesicles transporting protein and nucleic acid components), which are both released by cells and participate in inter-cellular communication. Specifically, we hypothesize that a) in human PBMCs, ionizing radiation elicits the release of circulating factors that modulate the negative effects of irradiation; b) cytokines and exosomes are the best candidate biomarkers for radiation, based on their association with radiation-induced responses and interpersonal variability; and c) cytokines and exosomes are the circulating factors participating in the transport of the radiation message from irradiated cells to unirradiated cells. We will address this hypothesis studying cytokine responses to gamma and high-linear energy transfer (LET) particle irradiation, across a genetically diverse population of 400 healthy individuals. We also aim to identify exosomal RNA and miRNA from human PBMC supernatants that are common indicators of responses to low and high-LET radiation. The respective role of cytokines and exosomes in the transport of the radiation risk across cells will be validated by investigating whether cytokines or exosomal content are sufficient to transmit the cellular outcomes of irradiation. While previous studies have identified either circulating biomarkers or exosomal components related to radiation exposure, here we propose to take into account the variation in individual sensitivity to radiation with the study of a large cohort, and to compare the respective effects of circulating vs. exosomal factors of irradiation. In addition, this study will be the first to investigate the cytokine and exosome expression a) by human primary cells and b) under space-relevant doses and types of irradiation. The proposed work is essential to the preparation of upcoming prolonged spaceflight and deep space habitation by identifying circulating blood biomarkers of radiation responses and understanding the physiological role of these biomarkers in the propagation of radiation-induced biological damages. Detection of radiation-related blood biomarkers will provide an easy and fast solution for individual diagnostics and risk prevention, while a better understanding of novel mechanisms involved in the spread of radiation-induced effects will enable to better target these mechanisms for preventive and therapeutic solutions with the perspective of protecting the crew from space radiation-induced biological risks.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This project is essential to the preparation of upcoming prolonged spaceflight and deep space habitation to protect the crew from space radiation-induced biological risks. This is addressed by identifying circulating biomarkers (cytokines and exosomes) of radiation responses and understanding the physiological role of these biomarkers in the propagation of radiation-induced biological damages. Detection of radiation-related cytokines and exosomal components in blood will provide an easy and fast solution for individual diagnostics and risk prevention, while a better understanding of novel mechanisms involved in the spread of radiation-induced effects will enable to better target these mechanisms for preventive and therapeutic solutions. While previous studies have identified either circulating biomarkers or exosomal components related to radiation exposure, here we benefit from our genomic association study of radiation responses in the largest human cohort to date to be studied in the context of space radiation exposure (786 donors), in order to take into account the variation in individual sensitivity to radiation. In addition, this study is the first to compare the respective effects of cytokines and exosomes released a) by human primary cells and b) under space-relevant doses and types of irradiation.
	Understanding the mechanisms underlying the human responses to space radiation is a high priority for upcoming lunar and Mars missions and could enable preventive actions and countermeasures to avoid radiation-induced risks. Peripheral blood lymphocytes have been commonly studied to evaluate radiation-induced biological responses since they are easily accessible, can provide individual assessment of radiation sensitivity, and are among the most radiosensitive cell types in the human body. Our laboratory aims at understanding the individual variability of human sensitivity to ionizing radiation, for the first time focusing on space-relevant high mass and charge (HZE) particle radiation based on DNA and cellular damage in Peripheral Blood Mononuclear Cells (PBMCs) and genomic associations. This project extends this ongoing study by identifying blood-based circulating factors regulating radiation responses in humans, which will provide better understanding of how radiation influences human health to develop countermeasures. We study radiation-induced damage in human immune cells following exposure to two types of space-relevant radiation (gamma ray and Fe particles), with a focus on expression changes and functional roles of two types of blood-based biomarkers: cytokines (small proteins) and exosomes (extracellular vesicles transporting protein and nucleic acid components), which are both released by cells and participate in inter-cellular communication. We hypothesize that a) in human PBMCs, ionizing radiation elicits the release of circulating factors that modulate the negative effects of irradiation; b) cytokines and exosomes are the best candidate biomarkers for radiation, based on their association with radiation-induced responses and interpersonal variability; and c) cytokines and exosomes are the circulating factors participating in the transport of the radiation message from irradiated cells to unirradiated cells. We address this hypothesis by 1) identifying circulating human cytokines that are significantly induced or repressed by exposure to gamma rays and Fe particles from a group of 400 genetically diverse individuals, 2) determining radiation-related exosomal components (RNAs and miRNAs) in PBMC exosomes after gamma and Fe irradiation in a group of 20 individuals, and 3) validating the physiological role of radiation-related circulating and exosomal factors on unirradiated PBMC population from 20 individuals. While previous studies have identified either circulating biomarkers

Task Progress:	or exosomal components related to radiation exposure, here we propose to take into account the variation in individual sensitivity to radiation with the study of a large cohort, and to compare the respective effects of circulating vs. exosomal factors of irradiation. In addition, this study is the first to investigate the cytokine and exosome expression a) by human primary cells and b) under space-relevant doses and types of irradiation. During the first year of this project, we found that: - Immune cytokines are significantly induced by exposure to Fe particles, specifically in individuals with low baseline level of spontaneous DNA damage: we quantified a panel of 32 standard human immune cytokines secreted over 24 hours following exposure to 1.1 and 3 particles/100 um2 of 600 MeV/n 56Fe irradiation in PBMC supernatant from 24 healthy donors (caucasian, 62% females/38% males, 19 - 68 years old, 20 - 47 body mass index (BMI)). Baseline DNA damage level was quantified using 53BP1+ immunocytochemistry in the total cohort of 768 healthy donors (caucasian, 50% females/50% males, 18 - 75 years old), and 24 donors were selected for cytokine analysis based on their significantly low or high baseline DNA damage (12 individuals per group). A very distinct cytokine response was observed in these two groups following Fe irradiation. No significant changes in cytokine expression for the 12 donors with high baseline DNA damage, but significant cytokine expression increase for the 12 donors with low baseline DNA damage. This indicates that lower baseline DNA damage correlates with enhanced cytokine signaling after irradiation. Exosome secretion is increased following exposure to gamma rays: we quantified the concentration of exosomes secreted over 24 hours following exposure to 0.5, 1, and 4 Gy of gamma irradiation in PBMC supernatant from 6 healthy donors. An increase in exosome concentration was observed for all donors after 4 Gy irradiation (significant for 4 donors out of 6), with no other significance at the two other doses tested. These findings confirm the hypothesis that ionizing radiation modulates the expression of immune cytokines and exosomes in human primary immune cells. We discovered that the magnitude of the cytokine response anti-correlates with the amount of baseline DNA damage initially present in PBMCs before irradiation, suggesting that low baseline subjects have better clearance of radiation-damaged cells, but could also be more prone to systemic inflammation and immune dysregulation. Specifically, cytokines that were overexpressed in low baseline subjects after irradiation are involved in hematopoiesis stimulation, immune progenitor proliferation and differentiation (Flt-3L, fibroblast growth factors-2 (FGF-2), epidermal growth factor (EGF)), adhesion and migration of differentiated immune cells (fractalkine), T helper type 1 (Th1) (interleukin (IL)-12p70, IL-15)), and Th2 (eotaxin, IL-13) lymphocyte-mediated immunity, anti-inflammatory responses (interferon (IFN)-a2, sCD40L), anti-tumorigenic activity (Tumor necrosis factor (TNF) beta)) and increased angiogenesis (FGF-2, vascular endothelial growth factor (VEGF)). In the coming year, we are planning to: - Compare the reported cytokine and exosome response to gamma rays (for cytokines) and Fe irradiation (for exosomes) at a later time point post-irradiation (48 h), and in the same cohort of 24 subjects with extreme low/high baseline DNA damage. - Perform transcriptomics of radiation-induced exosomes. - Study cellular responses of unirradiated PBMCs exposed to radiation-induced cytokines or exosomes.
Bibliography Type:	Description: (Last Updated: 12/15/2020)
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