Fiscal Year:	FY 2021	**Task Last Updated:**	FY 04/16/2021
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Project Title:	Space Radiation Exposure and Risk Mediated by Clonal Hematopoiesis		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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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Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2019-2020 HERO 80JSC019N0001-HHCBPSR, OMNIBUS2: Human Health Countermeasures, Behavioral Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D
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Flight Program:			
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Task Description:	During spaceflight, astronauts are exposed to many stresses that alter multiple physiological systems. The recent NASA Twin Study provided a highly detailed analysis of how prolonged, low orbit space travel may contribute to genotoxic stress, elevated DNA damage responses and genomic instability in leukocytes. The observed genomic instability during and after flight suggests that the ionizing radiation exposure caused DNA damage to hematopoietic stem cells that replenish blood cells throughout life. Thus, it is conceivable that these alterations will contribute to the development of hematologic malignancies and other chronic diseases through changes in immune cell function. Furthermore, these effects may be particularly magnified when traveling beyond Earth's geomagnetic field where there is increased exposure to high atomic number and high energy radiation. Recent epidemiological studies have documented the prevalence of somatic mutations within the cells of the hematopoietic system in healthy individuals. These acquired DNA mutations accumulate with age and, in some instances, can provide a competitive advantage to the mutant cell thus allowing for its clonal expansion, a phenomenon known as clonal hematopoiesis of indeterminate potential (CHIP). While the mutational landscape of CHIP has only partially been deciphered, some of these clonal expansions can be attributed to somatic mutations in driver genes that are recurrently mutated in blood malignancies. These driver genes include epigenetic regulators (TET2, DNMT3A, ASXL1), spliceosome components (SF3B1, SRSF2), signaling proteins (JAK2), and DNA damage response molecules (TP53, PPM1D). Studies show that CHIP is associated with an increased risk of all-cause mortality. While there is a marked increase in the frequency of hematological cancer in individuals with CHIP, which is to be expected, the major cause of the increased mortality in these populations appears to be an increase in cardiovascular diseases including coronary heart disease, stroke, and early-onset myocardial infarction. Studies in the applicants' laboratories have provided evidence for a causal link between CHIP, derived from mutations in TET2, DNMT3A, or JAK2 genes, and cardiovascular, metabolic, and renal pathologies. In one instance, it was shown that the pathological effects of a CHIP driver mutation (TET2) could be mitigated with a specific anti-inflammatory drug. Of particular relevance to the proposed studies, there is an accelerated form of clonal hematopoiesis that is observed in individuals that have undergone myelosuppressive treatment and is referred to as "therapy-related clonal hematopoiesis." Under these conditions, it has been shown that there are hematopoietic clonal expansions with a very high frequency of mutations in PPM1D andTP53, both of which are classic DNA damage response genes. In individuals undergoing cytotoxic therapy, the hematopoietic system is likely under extreme stress, and it is thought that mutations in genes such as TP53 and PPM1D confer the mutated hematopoietic stem cell with a survival advantage against genotoxic stress induced by chemotherapy. Recent work from the applicants' laboratories have shown that this form of CHIP can synergize with the genotoxic agent's direct effect on the cardiovascular system to promote a more robust cardiomyopathic phenotype. While the impact of space travel on CHIP is completely unknown, it is reasonable to speculate that space radiation in combination with other space travel-related stresses will lead to radiation-specific and gene-specific accelerations of clonal hematopoiesis. Further, these forms of CHIP may increase the risk of leukemogenic and cardiovascular pathologies in a radiation- and gene-specific manner.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	New project for FY2021.
Bibliography Type:	Description: (Last Updated: 05/16/2025)