Fiscal Year:	FY 2022	**Task Last Updated:**	FY 11/24/2021
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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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Zip Code:	22903-3390	**Congressional District:**	5
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
Start Date:	01/29/2021	**End Date:**	01/28/2025
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	3	**No. of Master' Degrees:**	1
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	November 2021 report: N/A		
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Task Description:	During spaceflight, astronauts are exposed to many stresses that alter multiple physiological systems. The recent NASA Twins 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. This phenomenon is 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, JAK2, TP53 and PPM1D genes, and cardiovascular, metabolic, and renal pathologies. In some instances, it was shown that the pathological effects of a CHIP driver mutation (TET2, TP53 and PPM1D) could be mitigated with specific anti-inflammatory drugs. 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:	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.
Task Progress:	During our first year we were able to participate in the Summer 2021 NASA Space Radiation Laboratory (NSRL) campaign. In the months leading up to this campaign we prepared the mice that were used as bone marrow donors. Recipient mice (B6.SJL-Ptprca Pepcb/BoyJ) were purchased from Jackson Laboratory. These 96 mice received TP53 mutant or wild type bone marrow cells via the murine adoptive transfer bone marrow transplant (BMT) approach. Approximately 2 months after bone marrow transplantation, the mice were transported to Brookhaven National Laboratory (BNL) and exposed to one of four types of radiation: no radiation, 100cGy gamma, 100cGy simGCRsim, or 100cGy SPEsim. One member of the Walsh lab traveled to BNL to complete these irradiation sessions. After the irradiation sessions the mice were transported back to the University of Virginia and we are completing serial blood sampling and echocardiography. Thus far, in additional to baseline sampling, this cohort of mice has had flow cytometry and whole blood analysis performed at 1 month post-irradiation and 4 months post-irradiation. Echocardiography was performed before irradiation and the next time point will be in December 2021, 6 months post irradiation. Body weights are measured monthly. Going forward we plan to complete flow cytometry and whole blood analysis every 3-4 months and echocardiography every 6-8 months. In planning for future studies, we submitted proposals for the Spring 2022 and Summer 2022 NSRL campaigns. We were unable to submit a proposal for the Fall 2021 campaign because originally the GCR (galactic cosmic radiation) simulator was going to be unavailable for maintenance. When the maintenance schedule changed, and GCR became available during the Fall 2021 campaign, we did not have enough time to prepare donors and complete the bone marrow transplant before that campaign. At the end of October 2021 the Scientific Advisory Committee for Radiation Research approved our proposal to participate in the Spring 2022 NSRL campaign. Currently, we are preparing the Ppm1d mice that will be used as bone marrow donors for this set of experiments. Recipient mice will be ordered from Jackson Laboratory at the first of the year and the bone marrow transplant will take place approximately 2 months before we are scheduled to irradiate during the Spring 2022 campaign. For this Ppm1d cohort we will follow the same sampling schedule as discussed above for the TP53 cohort. In the next few months we hope to receive approval for the Summer 2022 NSRL campaign. As soon as we receive this approval we will start to prepare the Tet2 mice that will be used as bone marrow donors for this set of experiments. We expect this to be around the beginning of March 2022. In addition to the NSRL studies, we have been performing irradiation pilot studies at our facility to gain more insight into how various genes, including Tp53, Ppm1d, Tet2, and Dnmt3a, react to the stresses of radiation exposure. The findings of these pilot studies will potentially provide direction for the large cohort to be used in NSRL studies.
Bibliography Type:	Description: (Last Updated: 01/03/2024)

Articles in Peer-reviewed Journals	Yura Y, Walsh K. "Therapy-related clonal hematopoiesis: A new link between cancer and cardiovascular disease." Shinzo. 2022 Feb;54:268. , Feb-2022
Articles in Peer-reviewed Journals	Bisserier M, Shanmughapriya S, Rai AK, Gonzalez C, Brojakowska A, Garikipati VNS, Madesh M, Mills PJ, Walsh K, Arakelyan A, Kishore R, Hadri L, Goukassian DA. "Cell-free mitochondrial DNA as a potential biomarker for astronauts' health." J Am Heart Assoc. 2021 Nov 2;10(21):e022055. https://doi.org/10.1161/JAHA.121.022055 ; PubMed PMID: 34666498; PMCID: PMC8751818 , Nov-2021