

Fiscal Year:	FY 2023	Task Last Updated:	FY 11/21/2022
PI Name:	Walsh, Kenneth Ph.D.		
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		
PI Email:	kw9ar@virginia.edu	Fax:	FY
PI Organization Type:	UNIVERSITY	Phone:	434-243-8303
Organization Name:	University of Virginia, Charlottesville		
PI Address 1:	Hematovascular Biology Center		
PI Address 2:	415 Lane Rd, PO Box 801394, Suite 1010		
PI Web Page:			
City:	Charlottesville	State:	VA
Zip Code:	22903-3390	Congressional District:	5
Comments:			
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No. of Post Docs:	2	No. of PhD Degrees:	
No. of PhD Candidates:	3	No. of Master' Degrees:	1
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No. of Bachelor's Candidates:		Monitoring Center:	NASA JSC
Contact Monitor:	Elgart, Robin	Contact Phone:	281-244-0596 (o)/832-221-4576 (m)
Contact Email:	shona.elgart@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	Per the Principal Investigator (PI): Dr. Soichi Sano, M.D., Ph.D. has left the project. Dr. Megan Evans (University of Virginia, Charlottesville) was added to the project for her expertise in animal models of clonal hematopoiesis. (Ed, 1/6/23)		
COI Name (Institution):	Garrett-Bakelman, Francine M.D., Ph.D. (University of Virginia, Charlottesville) Hirschi, Karen Ph.D. (Yale University) Goukassian, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai) Evans, Megan A (University of Virginia)		
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Task Description:	<p>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.</p> <p>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).</p> <p>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.</p> <p>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 and TP53, 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.</p>
	Rationale for HRP Directed Research:
	Research Impact/Earth Benefits:
	<p>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.</p>
	<p>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 deoxyribonucleic acid (DNA) damage responses, and genomic instability in leukocytes. The observed genomic instability during and after flight suggests that 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 developing 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 numbers and high-energy radiation.</p> <p>During our second year, we were able to participate in the Spring and Summer 2022 NASA Space Radiation Laboratory (NSRL) campaigns. In the months leading up to this campaign, we prepared the mice that were used as bone marrow donors. Recipient mice were purchased from Jackson Laboratory. Ninety-six of these recipient mice received PPM1D mutant or wild-type bone marrow cells, via the murine adoptive transfer bone marrow transplant (BMT) approach. Another 96 recipient mice received TET2 KO, or wild-type bone marrow cells via the murine adoptive transfer 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. Currently, the PPM1D cohort is 7 months post-radiation exposure, and the TET2 cohort is 5 months post-radiation exposure. Thus far, in addition to baseline sampling, these cohorts of mice have had flow cytometry and whole blood analysis performed at 1-month post-irradiation, 4 months post-irradiation and then every 3-4 months. Echocardiography was performed before irradiation and approximately every 6 months after that. Body weights are measured monthly. In addition to these 2 cohorts, we continued to monitor and perform serial sampling for the TP53 cohort, which is currently 17 months after radiation exposure.</p> <p>The longest-running investigation (initiated in 2021) involves the analysis of male and female mice that had undergone adoptive transfer/bone marrow transplantation with the Trp53R270H mutation that is equivalent to the hotspot mutation R273H located at the DNA-binding domain of human TP53 (see Sano et al., JCI Insight, 2021). In the male TP53 cohort, the effect of radiation on mutant cell expansion in white blood cells (WBCs) was strongest in the following order: gamma and simGCRsim, followed by SPesim. In the female mutant cohorts, the effect of radiation was strongest with gamma, and SPesim and simGCRsim were slightly less. Overall, donor chimerism appears to be greater in the female groups compared to the male groups.</p> <p>Based on the ongoing analyses of these TP53 results, we extended the follow-up time from the originally proposed 12 months to approximately 18 months to highlight the age-, radiation-, and sex-dependent phenotypes observed in this</p>

<p>Task Progress:</p>	<p>cohort.</p> <p>To date, 21 of 96 mice have been removed from the TP53 cohort. The male mutant gamma and male mutant simGCRsim groups showed decreased survival over the other male mutant groups and all of the female groups. Necropsy of the animals from the TP53 cohort (mostly males) revealed that these mice are expiring from the consequences of hematologic malignancies. A general examination showed that mice exhibit one or more of the following general morphometric phenotypes: enlarged thymus, enlarged abnormally colored liver, enlarged abnormally colored kidneys, enlarged spleen, enlarged lymph nodes, enlarged heart, and obvious anemia. An analysis of blood cell counts over time (up to 12 months post-irradiation—with more time points to follow) revealed one or more of the following phenotypes: severe reductions in white blood cells, monocytes, neutrophils and lymphocytes, or large fluctuations in these parameters (increases followed by decreases, etc.), and large increases in eosinophil content. While some mice displayed enlarged and discolored hearts, serial echocardiographic analyses revealed little or no changes in cardiac contractility. Finally, evaluation by Dr. Eric Pietras (Hematology/Oncology, University of Colorado) provided the following potential diagnoses: bone marrow failure with multi-lineage dysplasia, acute myeloid leukemia or myeloproliferative neoplasia, and possible eosinophilic leukemia (rare). It is well known that men have a higher risk of developing hematologic malignancies or a shorter latency from initiation to diagnosis. The mechanism underlying this sex effect is largely unknown. The TP53 adoptive transfer/irradiation model appears to amplify the sex difference, and it may represent a useful model for understanding the molecular basis for these effects.</p> <p>In the PPM1D cohort, the effect of radiation on mutant cell expansion in WBCs follows similar trends as the TP53 cohort. In both the male and female groups, gamma and simGCRsim show the greatest expansion of the mutant cells. At 0 through 1-month post-irradiation, this expansion is greatest in the myeloid populations, but then at 1-4 months, the expansion is greatest in lymphoid populations (T and B cells). Similar to what was observed with the TP53 cohort, there appears to be a sex-specific effect where overall donor chimerism appears to be greater in the female groups compared to the male groups. To date, no mortality has occurred in the PPM1D cohort.</p> <p>In the TET2 cohort, the effect of radiation on mutant cell expansion in WBCs does not appear to be radiation specific. The mutant cell expansion occurs at the same rate regardless of the radiation type. To date, no mortality has occurred in the TET2 cohort.</p> <p>Going forward, we plan to continue flow cytometry and whole blood analysis every 3-4 months and echocardiography every 6-8 months for the PPM1D, TET2, and TP53 cohorts. The mice remaining in the TP53 cohort will be sacrificed, and tissues harvested in December 2022 or early January 2023. It will be of interest to determine whether the PPM1D and TET2 groups exhibit radiation-induced hematologic disorders and whether there is a strong sex bias, as was seen with TP53.</p> <p>In planning for future studies, we received approval to irradiate another cohort of mice in the Spring/Summer 2023 campaign. Most likely, this new cohort will examine a model of DNMT3A-mediated clonal hematopoiesis, which is the most prevalent form of clonal hematopoiesis observed in humans.</p> <p>Going forward, we also plan to repeat aspects of the TP53 cohort.</p> <p>It may also be of interest to examine the effects of mosaic loss of the Y chromosome (mLOY) in hematopoietic cells. mLOY is the most prevalent post-zygotic mutation in men. The prevalence of mLOY increases with age and, in the UK Biobank, ~45% of men exhibit appreciable mLOY by age 70. mLOY has been associated with increased mortality, cancer, and cognitive diseases. Epidemiological studies suggest that the mortality associated with mLOY can largely explain the 5-year difference in lifespan between men and women. Recently, we documented that men with mLOY exhibit an increased risk of mortality from cardiovascular diseases (S. Sano et al, Science. 2022. 377:292). This study also established, for the first time, a murine model of mLOY, and experiments with this model provided mechanistic evidence for a causal relationship between mLOY and morbidity and mortality.</p> <p>The pathological consequences of LOY secondary to ionizing radiation are completely unknown. Thus, in addition to the proposed NSRL studies, we have been performing gamma-irradiation pilot studies at our facility (UVA) to gain more insight into how mLOY reacts to the stresses of radiation exposure. These new studies represent the first analysis of LOY cell expansion in the murine adoptive transfer model and the first analysis of the effects of radiation on the expansion of LOY hematopoietic cells. The results of this pilot study indicate that hematopoietic mLOY cell expansion may be highly responsive to radiation, indicating that the murine mLOY model may be of interest for future NSRL studies.</p>
Bibliography Type:	Description: (Last Updated: 01/03/2024)
Articles in Peer-reviewed Journals	Bisserier M, Saffran N, Brojakowska A, Sebastian A, Evans AC, Coleman M, Walsh K, Mills PJ, Garikipati VNS, Arakelyan A, Hadri L, Goukassian DA. "Emerging role of exosomal long non-coding RNAs in spaceflight-associated risks in astronauts." Front Genet. 2022 Jan 17;12:812188. https://doi.org/10.3389/fgene.2021.812188 ; PubMed PMID: 35111205 ; PMCID: PMC8803151 . , Jan-2023
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