Task Book Report Generated on: 05/05/2024

Project Title: Space Radiation Exposure and Risk Mediated by Clonal Hematopoiesis Program/Discipline: Program/Discipline: Program/Discipline: Program/Discipline: Program/Discipline: Program/Discipline: Program/Discipline: Ident 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 Element: None Space Biology Special Category: None Pl Email: Resolvent Space Radiation Carcinogenesis Space Biology Special Category: None Pl Email: Resolvent Space Radiation Space Resolvent Space Radiation Carcinogenesis Pl Address: Pry Pl Organization Type: University of Virginia, Charlottoeville Pl Address 1: Hematovascular Biology Center Pl Address 2: Hematovascular Biology Center Pl Address 3: Hematovascular Biology Center Pl Address 4: 415 Lance Rd, PO Box 801394, Suite 1010 Pl Web Page: City: Charlotteeville State: VA Zip Code: Space Space Space Congressional District: 5 Comments: Comments: Solicitation / Funding OMNRISCE: Human Health Countermeasures, Space Resolution-Appendix C; Omnibus2-Appendix D Start Date: 0129/2021 End Date: 0129/2025 No. of Pab Degrees: 1 No. of Pab Candidates: No. of Pab Degrees: 1 No. of Pab Candidates: No. of Bachelor's 1 No. of Master's Candidates: Monitoring Center: NASA JSC Contact Monitor: Elgat, Robin Contact Phone: 281-244-0596 (a)832-221-4576 (m) Contact Monitor: Space Resolution Appendix C, Omnibus2-2416 (Fiscal Year:	FY 2022	Task Last Updated:	FY 11/24/2021
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Human Research Program Risks: (1) Cancer-Risk of Radiation Carcinogenesis Space Biology Cross-Element None Space Biology Cross-Element Space Biology Cross-Element Space Biology Special Category: None PI Email:	Joint Agency Name:		TechPort:	No
Space Biology Cross-Element Space Biology Cross-Element Disciplines Space Biology Special Category: None PI Email: Kw9an@virgania.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: Hematovascular Biology Center PI Address 2: Charlottesville State: City: Charlottesville State: VA Zip Code: 22903-3390 Congressional District: Comments: Project Type: OROUND Solicitation / Funding ONNIBUS2: Human Health Countermeasures, Source: Behavional Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D Start Date: 01/29/2021 End Date: 01/28/2025 No. of Pab Does: 2 No. of PhD Degrees: No. of PhD Degrees: 1 No. of Bachelor's 1 Degrees: No. of Bachelor's Candidates: No. of Bachelor's Candidates: Monitoring Center: NASA JSC Contact Email: shona-cleartionass gov Flight Program: Flight Assignment: Key Personnel Changes/Previous PI: November 2021 report: N/A Carrett-Backman, Fnancine M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Fleptormance Goal No:	Human Research Program Elements:	(1) SR:Space Radiation		
Space Biology Cross-Element Discipline: None PI Email: Kw9an@virginin.edu Fax: FY Pl 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: Comments: Project Type: GROUND Solicitation / Funding Solicitation / Funding OMNIBUS2: Human Health Countermeasures, Source: Behavioral Performance, and Space Relation-Appendix C; Omnibus2-Appendix D Start Date: 01/29/2021 End Date: 01/28/2025 No. of Post Does: 2 No. of Post Does: No. of Bachelor's No. of Bachelor's Degrees: No. of Bachelor's Candidates: No. of Bachelor's Candidates: No. of Bachelor's Candidates: No. of Bachelor's Candidates: Monitoring Center: NASA JSC Contact Email: shone-leart@mss.gov Flight Program: Flight Assignment: Key Personnel Changes/Previous PI: November 2021 report: N/A Gärett-Backman, Francine M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karne Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Hirrschi, Karne Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Flierth-Grormance Goal No:	Human Research Program Risks:	(1) Cancer: Risk of Radiation Carcinogenesis		
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Pl Organization Type: UNIVERSITY Phone: 434-243-8303 Organization Name: University of Virginia, Charlottesville Pl Address 1: Hematovascular Biology Center Pl Address 2: 415 Lane Rd, PO Box 801394, Suite 1010 Pl Web Page: City: Charlottesville State: VA Zip Code: 22903-3390 Congressional District: 5 Comments: Comments: GROUND Solicitation / Funding OMNIBUS2: Human Health Countermeasures, Source: Behavioral Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D Start Date: 01/29/2021 End Date: 01/28/2025 No. of Post Does: 2 No. of PhD Degrees: No. of PhD Candidates: No. of Master' Degrees: 1 No. of Master's Candidates: No. of Master' Degrees: 1 No. of Master's Candidates: Monitoring Center: NASA JSC Contact Monitor: Elgart, Robin Contact Phone: 281-244-0596 (o)/832-221-4576 (m) Contact Email: shons elgart@nasa.sov Flight Assignment: Key Personnel Changes/Previous PI: November 2021 report: N/A COI Name (Institution): Garrett-Balelman, Francine M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (University of Virginia, Charlottesville) Gorwassan, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai)	Space Biology Special Category:	None		
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: Project Type: GROUND Solicitation / Funding Source Behavioral Parcjourance, and Space Rediation-Appendix C; Omnibus 2-Appendix D Start Date: 01/29/2021 End Date: 01/28/2025 No. of Post Doors: 2 No. of PhD Degrees: 1 No. of PhD Candidates: 3 No. of PhD Degrees: 1 No. of Master's Candidates: 3 No. of Master' Degrees: 1 No. of Master's Candidates: No. of Bachelor's Candidates:	PI Email:	kw9ar@virginia.edu	Fax:	FY
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: Project Type: GROUND Solicitation / Funding OMNIBUS2: Human Health Countermeasures, Source: Behavioral Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D Start Date: 01/29/2021 End Date: 01/28/2025 No. of PhD Candidates: 2 No. of PhD Degrees: 1 No. of Master's Candidates: 3 No. of Master' Degrees: 1 No. of Master's Candidates: No. of Master' Degrees: 1 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 clgart@nasa.gov Flight Program: Flight Assignment: Key Personnel Changes/Previous PI: November 2021 report: N/A Garrett-Bakclman, Francine M.D., Ph.D. (University of Virginia, Charlottesville) Grant/Contract No.: 80NSSC21K0549 Performance Goal No.:	PI Organization Type:	UNIVERSITY	Phone:	434-243-8303
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: Project Type: GROUND Solicitation / Funding 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 Does: 2 No. of PhD Degrees: 1 No. of Post Does: 3 No. of Master' Degrees: 1 No. of Master's Candidates: No. of Bachelor's Degrees: 1 No. of Bachelor's Candidates: No. of Bachelor's Degrees: 1 No. of Bachelor's Candidates: Monitoring Center: NASA JSC Contact Monitor: Elgart, Robin Contact Phone: 281-244-0596 (o)/832-221-4576 (m) Schona-cleart@nasa.gov Flight Program: Flight Assignment: Key Personnel Changes/Previous PI: November 2021 report: N/A Garrett-Bakelman, Francine M.D., Ph.D. (University of Virginia, Charlottesville) Goulassian, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai) Grant/Contract No.: 80NSSC21K0549 Performance Goal No.:	Organization Name:	University of Virginia, Charlottesville	:	
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COI Name (Institution): Hirschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Goukassian, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai) 80NSSC21K0549 Performance Goal No.:	Key Personnel Changes/Previous PI:	November 2021 report: N/A		
Performance Goal No.:	COI Name (Institution):	Hirschi, Karen Ph.D. (Yale University) Sano, Soichi M.D., Ph.D. (University of Virginia, Charlottesville) Goukassian, David M.D., Ph.D. (ICAHN School of Medicine at Mount Sinai)		
	Grant/Contract No.:	80NSSC21K0549		
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Task Book Report Generated on: 05/05/2024

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).

Task Description:

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:

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