Fiscal Year:	FY 2022	**Task Last Updated:**	FY 08/27/2021
PI Name:	Hada, Megumi Ph.D.		
Project Title:	Combined Effects of Simulated Microgravity and Space Radiation on Human Cells		
Division Name:	Space Biology		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	(1) Cell & Molecular Biology (2) Animal Biology: Vertebrate		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	(1) Cell Culture (2) Translational (Countermeasure) Potential		
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Zip Code:	77446	**Congressional District:**	10
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2016-17 Space Biology (ROSBio) NNH16ZTT001N-FG. App G: Flight and Ground Space Biology Research
Start Date:	10/26/2018	**End Date:**	10/27/2022
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	1	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA KSC
Contact Monitor:	Zhang, Ye	**Contact Phone:**	321-861-3253
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 10/27/2022 per NSSC information (Ed., 9/15/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Wang, Jing Ph.D. (University of Texas MD Anderson Cancer Center) Takahashi, Akihisa Ph.D. (Gunma University Heavy Ion Medical Center, Japan) Fujiwara, Keigi Ph.D. (University of Texas MD Anderson Cancer Center)		
Grant/Contract No.:	80NSSC19K0133		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Space radiation and microgravity are two major environmental stressors for human in space travel. One of the fundamental questions in space biology research is whether the combined effects of microgravity and exposure to cosmic radiation are synergistic. While studies addressing this question have been carried out for half a century in space or using simulated microgravity on the ground, the reported results are conflicting. Although the reason for the variation in results is not known, it is possible that it may be due to the diversity of biological systems used but more importantly to the experimental designs and hardware used in these studies. For the assessment and management of human health risks in future Moon and Mars Missions, it is necessary to obtain more basic data on the molecular and cellular responses to combined effects of radiation and microgravity. To establish a firm baseline database, we propose to undertake a systematic study on cultured mammalian cells' responses to the simultaneous insult of radiation and microgravity (both immediate and long term) to elucidate the molecular signaling pathways that lead to these biological effects. The results of the study will provide cellular and molecular biological bases for the assessment and management of human health risks in space. Recently Dr. Takahashi, co-investigator of this proposal, has developed microgravity-irradiation systems consisting of a 3D clinostat synchronized to the carbon-ion or X-ray irradiation systems. Our new experimental setup allows us to avoid stopping clinostat rotation during irradiation, which was required in all other previous experiments. Gunma University Heavy Ion Medical Center is the only facility in the world where we can expose samples to high-linear energy transfer (LET) irradiation as well as low-LET irradiation under the simulated microgravity condition (i.e., without interrupting clinostat rotation). Our preliminary data obtained from the use of this new device on gene expression in human fibroblasts show that splicing cycle-related genes and cell cycle related genes are significantly up-regulated and S-phase DNA replication and DNA repair-related genes were down-regulated with C-ion irradiation under simulated microgravity. In this proposal we will investigate 3 different endpoints from early to late responses in 2 human cell lines using our new devices to study combined effects of microgravity and space radiation. Human fibroblasts and epithelial cells will be exposed to X-rays and C-ions under the simulated microgravity condition (rotated with 3-D clinostat). Control cells will be irradiated in 1G environment (with the static stage). We will investigate the extent of expression of specific proteins and of the post-translational modification states of signaling proteins (Aim 1), gene expressions and the pathways involved (Aim 2), and the extent of chromosome aberrations (Aim 3) caused by the combined effects of simulated microgravity and radiation. To investigate from the early to late endpoints in the same cell types will provide cellular and molecular biological data that are needed to understand the impact of combined effects of simulated microgravity and space radiation on human health. One of the selected endpoints is chromosome aberration, which is a well-established biomarker for cancer risk and has been used by NASA for the risk assessment of astronauts. Studying this endpoint allows us to compare our results to the astronauts' data after their International Space Station missions. Completion of this proposal will allow us to determine how the combination of microgravity and radiation will affect the transcriptomic, metabolomic, and proteomic states of cells as well as heritable changes in DNA. These finding will allow us to help develop the countermeasures for the future space missions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Completion of this proposal will allow us to determine how the combination of microgravity and radiation will affect the transcriptomic, metabolomic, and proteomic states of cells as well as heritable changes in DNA. These findings will allow us to help develop the countermeasure for the future space missions.
Task Progress:	Post-translational modification of proteins. Gravity is a vector, having both directionality and magnitude. During the 2nd year of investigation, we studied cellular response to μG. Under the μG condition, the gravity vector becomes virtually 0, losing both directionality and magnitude. In the 3rd year, we studied whether cells are able to respond only to changes in the gravity directionality. To answer this question, we cultured mammalian cells (mouse 3T3 cells and human and bovine endothelial cells) in tissue culture dishes and then the dishes were flipped upside down for up to 2 hours. We studied the upside down cells by microscopy and reverse-phase protein array (RPPA). Cultured cells were harvested after 0 (no flipping), 10, and 30 min of being upside down, and cell lysates were made. These lysates were then submitted to the MD Anderson's Proteomics Core for RPPA analyses using the standard array consisting of 488 antibodies. These data are now being analyzed. A manuscript preparation is under way. Gene expressions On the basis of our RNA-seq results, we are proceeding data analysis focusing on human aging-related genes. Nine genes (ARIDIA, CIS, COL1A1, COL3A1, PHF3, SMAD2, TPP1, TXNIP, ZFR) were calculated by considering the effect of simulated μG alone. Chromosome aberrations Using μG-irradiation system, human whole blood was exposed to X-rays and carbon ions under the simulated μG condition, and chromosomes of lymphocytes were collected with the premature chromosome condensation method in the first mitosis. Chromosome aberrations (CA) were quantified by the 3-color fluorescent in situ hybridization method. Cells exposed to irradiation under the simulated μG condition showed a higher frequency of both simple and complex type of CA compared to cells irradiated under the static condition by either X-rays or carbon-ions. Manuscript has been published with these results (See Biol Sci Space listing in Bibliography section below).
Bibliography Type:	Description: (Last Updated: 02/07/2024)
Abstracts for Journals and Proceedings	Ikeda H, Muratani M, Hidema J, Hada M, Fujiwara K, Souda H, Yoshida Y, Takahashi A. "3D clinostat synchronized irradiation systems and expression profile changes of cell cycle-related genes in human fibroblasts." Presented at the 63rd Annual Meeting of the Japanese Radiation Research Society (JRRS), Fukushima Japan (Virtual Meeting), October 15-16, 2020. Abstract book of Japanese Radiation Research Society (JRRS) 2020 meeting, October 2020. , Oct-2020

Abstracts for Journals and Proceedings	Yamanouchi S, Takeuchi K, Takahashi S, Tashiro M, Hidema J, Higashitani A, Adachi T, Zhang S, Guirguis FNL, Yoshida Y, Nagamatsu A, Hada M, Takeuchi K, Takahashi T, Sekitomi Y, Takahashi A. "Development of combined-environment simulator for low-dose-rate radiation and partial gravity of Moon and Mars." Presented at the 63rd Annual Meeting of the Japanese Radiation Research Society (JRRS), Fukushima Japan (Virtual Meeting), October 15-16, 2020. Abstract book of Japanese Radiation Research Society (JRRS) 2020 meeting, October 2020. , Oct-2020
Abstracts for Journals and Proceedings	Hada M, Yamanouchi S, Ikeda H, Rhone JR, Plante I, Fujiwara K, Saganti PB, Takahashi A. "Increased chromosome aberrations in cultured human fibroblasts and lymphoblastic cells exposed simultaneously to simulated microgravity and radiation." Presented at the 66th Annual Meeting of Radiation Research Society, Virtual Meeting, October 18-21, 2020. Abstract Book. 66th Annual Meeting of Radiation Research Society, Virtual Meeting, October 18-21, 2020. , Oct-2020
Abstracts for Journals and Proceedings	Hada M, Yamanouchi S, Rhone JR, Mao J-H, Ikeda H, Plante I, Fujiwara K, Saganti PB, Takahashi A. "Increases chromosome aberrations in human cells exposed simultaneously to simulated microgravity and radiation." Presented at 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. Abstract Book. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021
Abstracts for Journals and Proceedings	Takahashi A, Yamanouchi S, Takeuchi K, Takahashi S, Tashiro M, Hidema J, Higashitani A, Adachi T, Zhang S, Guirguis FNL, Yoshida Y, Nagamatsu A, Hada M, Takeuchi K, Takahashi T, Sekitomi Y. "Development of equipment simulating deep space, Moon and Mars." Presented at the 32nd Conference of the Japan Society of Microgravity Application, Virtual, October 7, 2020. Abstract Book. 2nd Conference of the Japan Society of Microgravity Application, October 7, 2020. , Oct-2020
Abstracts for Journals and Proceedings	Takahashi, Suzuki K, Chizuru C, Morioka T, Takeshima T, Yoshida Y, Nakamura A, Ikeda H, Hada M, Nagamatsu A, Ohira Y, Inatomi Y, Kakinuma S. "Research on Combined Effects of Space Radiation and Variable Gravity – 2020 Annual Report. " Presented at the 35th Space Utilization Symposium, Virtual, January 19, 2021. Abstract book of Space Utilization Symposium 2021, January 2021 , Jan-2021
Abstracts for Journals and Proceedings	Takahashi A. "Does cancer progress in space?" Presented at the Committee on Space Research (COSPAR) 2021-Hybrid, 43rd Scientific Assembly, Sydney, Australia, January 28-February 4, 2021. Abstract book of COSPAR 2021, January 28-February 4, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Yamanouchi S, Adachi T, Yoshida Y, Rhone J, Mao J-H, Fujiwara K, Saganti PB, Takahashi A, Hada M. "The combined effect of simulated microgravity and radiation on chromosome aberrations in human peripheral blood lymphocytes." Biol Sci Space. 2021;35:15-23. https://doi.org/10.2187/bss.35.15 , Aug-2021
Awards	Yamanouchi S. "President's award for outstanding research, Gunma University Graduate School of Medicine, March 2021." Mar-2021
Dissertations and Theses	Yamanouchi S. "Simultaneous exposure of cultured human lymphoblastic cells to simulated microgravity and radiation increases chromosome aberrations." Masters dissertation, Gunma University Graduate School of Medicine, Maebashi, Japan, March 2021. , Mar-2021