Fiscal Year:	FY 2024	**Task Last Updated:**	FY 08/21/2023
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		
PI Email:	mehada@pvamu.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	936-261-3155
Organization Name:	Prairie View A&M University		
PI Address 1:	College of Arts and Sciences, PO BOX 519, MS-2230, New Science Bldg		
PI Address 2:			
PI Web Page:			
City:	Prairie View	**State:**	TX
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:**	04/25/2023
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:		**No. of Master' Degrees:**	1
No. of Master's Candidates:	0	**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
Contact Email:	Ye.Zhang-1@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 04/25/2023 per NSSC information (Ed., 7/31/23) 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		
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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:	Gene Expressions: 1BR-hTERT human fibroblast cells were cultured under 1 gravity (1G) or simulated μG for 48 hrs in total and collected 0 (sham-irradiated), 3 or 24 hrs after X-ray or Carbon-ion (C-ion) irradiation. A three-dimensional clinostat was used to accomplish the simulation of μG and the simultaneous radiation exposure of the samples. In total, 36 samples were analyzed (12 conditions in triplicates). The raw transcriptomic data produced from these studies were reanalyzed in the current work, applying a systems biology approach, to identify all differentially expressed genes (DEG) between various conditions and the predominant processes they participate in, and to identify a possible synergy between radiation and μG. RNAseq, employing DESeq2, was the method used to produce lists of differentially expressed genes between different biological conditions. Over-representation analyses were performed in order to identify the enriched biological pathways and targeting transcription factors in up- and down-regulated genes from each DEG analysis. Comparing sham-irradiated cells under simulated μG and 1G conditions, terms related to response to oxygen levels and muscle contraction were identified. After irradiation with 1Gy of X-ray or C-ion or simulated μG condition, CDKN1A, MDM2, PURPL, PTCHD4, TP53INP1, PAPPA and BTG2 were found to be over-expressed, while MKI67, CCNB1, histone clustered genes, and minichromosome maintenance genes were found to be under-expressed. Prevailing biological processes in DEGs upon irradiation were related to DNA damage repair, signal transduction by p53 class mediator, cell cycle arrest, and apoptosis. Chromosome Aberrations (CA): We have also reported our newly established "Simulator of the environments on the Moon and Mars with Neutron-irradiation and Gravity change" (“SwiNG”), for in vitro experiments (Takahashi et al., 2020) in last year’s report. [Ed. Note: See Cumulative Bibliography for complete reference.] Samples can be exposed to neutrons at a low-dose-rate (0.5 mGy/day) using Californium-252 in the center of the centrifuge. In this study, using this new device, human fibroblasts 1BR-hTERT were exposed to low dose neutrons for 5 days under the simulated outer space (μG), the Moon (1/6G), and Mars (3/8G) condition for 5 days, and chromosomes were collected by using the premature chromosome condensation methods. Chromosomes were analyzed with 3-color whole-chromosome FISH staining. Cells exposed to radiation and partial gravity simultaneously showed higher frequencies of CA compared to exposed to radiation under 1G.
Bibliography Type:	Description: (Last Updated: 06/26/2025)

Abstracts for Journals and Proceedings	Hada M, Ikeda H, Saganti PB, Takahashi A. "Increased chromosome aberrations in human cells exposed simultaneously to simulated microgravity and neutrons." 38th Annual Meeting of the American Society for Gravitational and Space Research, Houston, TX, November 9-12, 2022. Abstracts. 38th Annual Meeting of the American Society for Gravitational and Space Research, Houston, TX, November 9-12, 2022. , Nov-2022
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