Fiscal Year:	FY 2022	**Task Last Updated:**	FY 07/13/2023
PI Name:	Jahng, James Won Suk Ph.D.		
Project Title:	Countermeasure Development Against Myocardial Mitochondrial Stress by Space Radiation Exposure		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	94305	**Congressional District:**	18
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2021 TRISH-RFA-2101-PD: Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
Start Date:	09/01/2021	**End Date:**	08/31/2023
No. of Post Docs:	1	**No. of PhD Degrees:**	
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 08/31/2023 per TRISH (AvD, 7/13/23).		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Wu, Joseph M.D., Ph.D. (MENTOR: Stanford University)		
Grant/Contract No.:	NNX16AO69A-P0604		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Astronauts on long space missions are exposed to prolonged space radiation exposure which contains highly penetrable ionizing radiation and can cause serious cardiovascular complications. There are many uncertainties in assessing the biological effects of chronic space radiation exposure because space radiation is very distinct from terrestrial radiation such as X-rays or gamma rays. This is especially true when one is exposed to radiation at low dose. Currently, there are no effective countermeasures to prevent or treat space radiation induced health complications. The objective of this postdoctoral fellowship proposal is to develop novel and effective countermeasure against space radiation induced cardiovascular injury using induced pluripotent stem cells (iPSC). The invention of iPSCs has provided us an accessible, versatile, and adaptable source of stem cells which can be differentiated into any cell types we desire. I will generate cardiomyocytes from iPSCs and screen large number of chemical compounds for radioprotective drugs that preserve the contractility in iPSC cardiomyocytes under mitochondrial stress. Emerging evidence suggests that spaceflight environment causes mitochondrial dysfunction and mitochondrial stress response pathways that contribute to degenerative effects by radiation exposure. Once I identify candidate drugs, I will test them in heart-like organs which are engineered by mixing iPSC-derived cardiomyocytes, endothelial cells, and cardiac fibroblasts. In addition, 3D iPSC-derived engineered heart tissues will undergo chronic space radiation at low dose, and I will comprehensively characterize the functional and molecular changes occurring in engineered heart tissues after irradiation. I will use X-rays as a terrestrial control. Successful completion of this postdoctoral fellowship study will provide (i) study results of chronic space radiation exposure on human hearts and (ii) development of novel radioprotective countermeasure against space radiation-induced injuries. Reducing uncertainties in cardiovascular risks against space radiation will accelerate humanity’s dream to travel space.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	A ground-breaking discovery of pluripotent stem cells (iPSC) reprogramming has provided an accessible, versatile, and adaptable platform for precision medicine that we can study the changes at various biology systems and associate molecular signatures to disease phenotype or differential susceptibility to stressors. The current Translational Research Institute for Space Health (TRISH) fellowship aims to discover compounds that safely and effectively modulate the radiation induced cardiovascular disease by employing iPSC technology. With our established protocol to generate highly pure, mature and functional cardiomyocytes, we can systematically evaluate the efficacy of candidate drugs in preventing or modulating radiation induced cardiac dysfunction. Moreover, with the rich iPSC biobank resource available at Stanford Cardiovascular Institute, we can test the efficacy of candidate drugs in iPSC-derived cardiomyocytes from different genetic backgrounds.
Task Progress:	Astronauts on long space mission are exposed to prolonged exposure to space radiation which causes serious cardiovascular disease. However, there are no effective countermeasures to prevent or intervene ionizing radiation induced cardiovascular complications. The objective of current TRISH fellowship is to develop novel and effective countermeasure against ionizing radiation-induced cardiovascular injury using induced pluripotent stem cells derived cardiomyocytes (iPSC-CMs). iPSC-CMs from three different donors (comparable to astronaut demographics = Caucasian, male, 30s) were exposed to the different dose or X-rays radiation (0, 2, 5, 10 Gy) and various molecular parameters (viability, DNA-damage, oxidative stress, mitochondrial function) were measured at different times post irradiation (1 hour, 1 day, 3 day) and correlated the functional changes (beating rate, contraction velocity, relaxation velocity) at 14 days post irradiation. Prevailing mitochondrial dysfunction was observed at 3 days post irradiation and co-treatment with antioxidant significantly restored mitochondrial function in irradiated iPSC-CMs. Using oxidative stress as a primary screening parameter, we identified genistein or simvastatin robustly reversed reactive oxygen species (ROS) accumulation in iPSC-CMs following irradiation. We will further validate the efficacy of genistein and/or simvastatin on advanced 3D culture system (engineered heart tissues) or in a mouse model of radiation induced heart disease in upcoming 2022-2023 TRISH year. A successful completion of this postdoctoral fellowship study will provide (i) study results of chronic space radiation exposure on human hearts and (ii) development of novel radioprotective countermeasure against space radiation-induced injuries. Reducing uncertainties in cardiovascular risks against space radiation will accelerate a humanity’s dream to travel space.
Bibliography Type:	Description: (Last Updated: 01/12/2023)
Articles in Peer-reviewed Journals	Jahng JWS, Wu JC. "Cardiac reprogramming via chromatin remodeling by CRISPR activation." Mol Ther. 2022 Jan 5;30(1):6-7. https://doi.org/10.1016/j.ymthe.2021.12.005 . Epub 2021 Dec 10. PMID: 34895515; PMCID: PMC8753518 , Jan-2022
Articles in Peer-reviewed Journals	Nishiga M, Jahng JWS, Wu JC. "Ferroptosis of pacemaker cells in COVID-19." Circ Res. 2022 Apr;130(7):978-80. https://doi.org/10.1161/CIRCRESAHA.122.320951 . Epub 2022 Mar 31. PMID: 35357897 , Apr-2022