

<b>Fiscal Year:</b>	FY 2023	<b>Task Last Updated:</b> FY 11/05/2025	
<b>PI Name:</b>	Jahng, James Won Suk Ph.D.		
<b>Project Title:</b>	Countermeasure Development Against Myocardial Mitochondrial Stress by Space Radiation Exposure		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>			
<b>Program/Discipline--Element/Subdiscipline:</b>	TRISH--TRISH		
<b>Joint Agency Name:</b>		<b>TechPort:</b>	No
<b>Human Research Program Elements:</b>	None		
<b>Human Research Program Risks:</b>	None		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Zip Code:</b>	94305	<b>Congressional District:</b>	18
<b>Comments:</b>			
<b>Project Type:</b>	Ground	<b>Solicitation / Funding Source:</b>	2021 TRISH-RFA-2101-PD: Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
<b>Start Date:</b>	09/01/2021	<b>End Date:</b>	08/31/2023
<b>No. of Post Docs:</b>	1	<b>No. of PhD Degrees:</b>	
<b>No. of PhD Candidates:</b>		<b>No. of Master' Degrees:</b>	
<b>No. of Master's Candidates:</b>		<b>No. of Bachelor's Degrees:</b>	
<b>No. of Bachelor's Candidates:</b>	1	<b>Monitoring Center:</b>	TRISH
<b>Contact Monitor:</b>		<b>Contact Phone:</b>	
<b>Contact Email:</b>			
<b>Flight Program:</b>			
<b>Flight Assignment:</b>	NOTE: End date changed to 08/31/2023 per TRISH (AvD, 7/13/23).		
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Wu, Joseph M.D., Ph.D. ( MENTOR: Stanford University )		
<b>Grant/Contract No.:</b>	NNX16AO69A-P0604		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

**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.

**Task Description:**

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 missions face a significant health challenge—prolonged exposure to space radiation, which can lead to serious cardiovascular complications. At present, there are no effective measures to prevent or mitigate these ionizing radiation-induced cardiovascular issues. The current initiative under the TRISH fellowship strives to be at the forefront of pioneering innovative countermeasures against such injuries by utilizing induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).

In an effort to simulate real-world astronaut demographics, iPSC-CMs were cultivated from three distinct donors representing the typical astronaut characteristics, including age and ethnicity (SCVI-15, SCVI-621, SCVI-632). These iPSC-CMs were subjected to varying doses of X-ray radiation (ranging from 0 to 10 Gy) and underwent comprehensive functional and molecular assessments at multiple time points post-irradiation (1 hour, 1 day, 3 days, 7 days, and 14 days). The findings revealed that irradiation above 5 Gy led to a significant elevation in DNA damage and oxidative stress. Intriguingly, evidence of cell death or viability was not robust, indicating a relatively high radioresistance in cardiomyocytes compared to other cell types such as endothelial cells and fibroblasts. Notably, the increase in DNA damage and oxidative stress was transient, with all changes resolving within 24 hours. However, a notable and persistent effect emerged at 7 days post-irradiation, showcasing significant mitochondrial dysfunction, as indicated by alterations in respiratory oxygen consumption (basal respiration, ATP production, spare respiratory capacity).

These mitochondrial changes were not merely isolated events; they correlated with functional alterations, including a decreased beating rate, contraction velocity, and relaxation velocity at the 14-day mark post-irradiation with 5 Gy X-ray irradiation compared to the sham control. Concurrent treatment with the antioxidant N-acetylcysteine (NAC) at 1mM successfully restored mitochondrial function in the irradiated iPSC-CMs. This observation rationalized a focused drug screening effort on oxidative stress. Utilizing iPSC-CMs from a representative control line (SCVI-15), an extensive screening of a 2320-drug FDA-approved library was conducted. This effort led to the identification of honokiol as a potent agent. Honokiol, a polyphenolic natural compound with a small molecular weight, boasts a track record of demonstrating multiple health benefits, including anti-cancer, anti-inflammatory, and anti-hypertrophic effects. Importantly, honokiol has also been shown to activate SIRT3, a key regulator of enzymes related to mitochondrial function.

The research conducted so far has validated the efficacy of SIRT3 in reversing NAD<sup>+</sup> content and mitochondrial respiratory dysfunction in iPSC-CMs following irradiation. Looking ahead, the research team plans to further validate the effectiveness of honokiol in an animal model of chest irradiation in future experiments, aiming to bridge the gap between promising laboratory findings and potential translational applications. The successful completion of this postdoctoral fellowship study holds the promise of yielding two significant outcomes: firstly, it will provide valuable insights into the impact of chronic space radiation exposure on the human heart; and secondly, it will pave the way for the development of novel radioprotective measures against space radiation-induced injuries. Reducing uncertainties surrounding cardiovascular risks posed by space radiation is a crucial step toward realizing humanity's dream of space exploration.

**Bibliography Type:**

Description: (Last Updated: 11/05/2025)

Articles in Peer-reviewed Journals	Jahng JWS, Little MP, No HJ, Loo BW Jr, Wu JC. "Consequences of ionizing radiation exposure to the cardiovascular system." Nat Rev Cardiol. 2024 Dec;21(12):880-98. Review. <a href="https://doi.org/10.1038/s41569-024-01056-4">https://doi.org/10.1038/s41569-024-01056-4</a> ; PMID: <a href="https://pubmed.ncbi.nlm.nih.gov/38987578/">38987578</a> ; PMCID: <a href="https://pubmed.ncbi.nlm.nih.gov/PMC12037960/">PMC12037960</a> , Dec-2024
Articles in Peer-reviewed Journals	Lee S, Vander Roest AS, Blair CA, Kao K, Bremner SB, Childers MC, Pathak D, Heinrich P, Lee D, Chirikian O, Mohran SE, Roberts B, Smith JE, Jahng JW, Paik DT, Wu JC, Gunawardane RN, Ruppel KM, Mack DL, Pruitt BL, Regnier M, Wu SM, Spudich JA, Bernstein D. "Incomplete-penetrant hypertrophic cardiomyopathy MYH7 G256E mutation causes hypercontractility and elevated mitochondrial respiration." Proc Natl Acad Sci USA. 2024 May 7;121(19):e2318413121. <a href="https://doi.org/10.1073/pnas.2318413121">https://doi.org/10.1073/pnas.2318413121</a> ; PMID: <a href="https://pubmed.ncbi.nlm.nih.gov/38683993/">38683993</a> ; PMCID: <a href="https://pubmed.ncbi.nlm.nih.gov/PMC11087781/">PMC11087781</a> , May-2024