Fiscal Year:	FY 2022	**Task Last Updated:**	FY 10/28/2022
PI Name:	Weil, Michael Ph.D.		
Project Title:	Effects of Chronic High LET Radiation on the Human Heart		
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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City:	Fort Collins	**State:**	CO
Zip Code:	80521-2807	**Congressional District:**	4
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2020 TRISH Space Radiation Solicitation TSRAD-2020. Translational Research Institute for Space Health (TRISH) Human-Based Models to Study Effects of Space Radiation and Countermeasures
Start Date:	11/01/2020	**End Date:**	04/30/2024
No. of Post Docs:	3	**No. of PhD Degrees:**	
No. of PhD Candidates:	4	**No. of Master' Degrees:**	
No. of Master's Candidates:	2	**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 04/30/2024 per E. Urquieta/TRISH (Ed., 3/8/24). NOTE: Start/End dates changed to 11/1/2020 and 10/31/2023, respectively, per E. Urquieta/TRISH (Ed., 9/14/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Chatterjee, Anushree Ph.D. (University of Colorado at Boulder) Brandl, Alexander Ph.D. (Colorado State University) Chicco, Adam Ph.D. (Colorado State University) Wu, Joseph M.D., Ph.D. (Stanford University)		
Grant/Contract No.:	NNX16AO69A-RAD0105		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	We have detected adverse cardiac effects in mice and rats exposed to either high energy (HZE) ions or low dose rate neutrons, radiation exposures which simulate those in space. We propose to extend these findings to an engineered model of human cardiac tissue, identify biomarkers of radiation-induced cardiac damage, and test potential countermeasures against damage. To do this, we have assembled a team of experienced researchers from Colorado State University, Stanford University, and the University of Colorado. We will design and commission a facility that will allow us to expose engineered heart tissue (EHTs) to high linear energy transfer (LET) neutron radiation at low dose rate nearly continuously for more than a month. We will use the facility to irradiate EHTs fabricated using human induced pluripotent stem cells (hiPSCs) differentiated to cardiomyocytes, endothelium, and fibroblasts seeded into a fibrin/collagen-based extracellular matrix scaffold cast between flexible silicon posts. This is a robust physiological tissue model to identify functional and molecular changes, and we have previously flown hiPSC-derived cardiomyocytes aboard the International Space Station (ISS). Additional EHTs will be sham irradiated or irradiated with low dose rate gamma rays. The irradiated tissues will be screened for a panel of functional outcomes with known clinical relevance. Gene expression patterns will be determined to identify pathogenic gene networks that can be targeted with countermeasures, and media supernatants will be collected for metabolomics and proteomic analyses for biomarker discovery. Several small molecule countermeasures will be tested to attenuate adverse outcomes in the irradiated EHT based on published and preliminary studies in rodents and cell models. Among these is aspirin which targets oxidative stress, mitochondrial dysfunction and mtDNA damage, and inflammation implicated in our rodent models. We will also test overexpression of adeno-associated virus (AAV) transduced Nrf2 and antisense peptide nucleic acids (PNAs) directed against gene pathways identified in transcriptomic analyses as a novel and rapid multiplexed genetic countermeasure approach. Results from this proposed study will have the potential to improve risk assessments for space radiation induced cardiovascular disease, lead to methodologies for inflight detection for cardiac damage which, in turn, will inform decisions on whether countermeasures should be administered to individual crew members, and lead to the identification of those countermeasures.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This project has generated a human EHT model in the past calendar year, which had been used to study radiation-induced cardiotoxicity. We proved the feasibility of using this heart model for the deployment of radioprotective drugs.
Task Progress:	The aims of this project are to: 1. Develop a neutron irradiation resource that will enable complex tissue models to be chronically exposed to space-relevant, protracted high LET radiation at low-dose rate. 2. Characterize the damage to model cardiac tissues irradiated with low-dose rate neutrons and gamma rays with the intent of establishing relative biological effectiveness (RBE) for those types of damage with potential clinical consequences. 3. Use the model to identify biomarkers, particularly circulating biomarkers, for early detection of cardiac damage. Use the model to test potential countermeasures against cardiac dysfunction and damage. Our key findings are that a space-relevant dose of gamma ray radiation delivered at low-dose rate causes mitochondrial damage and respiratory dysfunction in cultured human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes, fibroblasts, and hiPSC-derived engineered heart tissues (EHTs). Contractile function of EHTs was also impaired. Shifts in the fibroblast and EHT transcriptome correlate with observed functional defects, particularly genes related to mitochondrial function, oxidative stress and DNA damage. Proof-of-concept countermeasure studies demonstrated protective effects of a mitochondria-targeted antioxidant (MitoTEMPO) against gamma radiation-induced damage in a human fibroblast cell line, which have now been extended to human engineered heart tissues (EHTs). Initial testing also indicated antisense peptide nucleic acids (PNA FASTmers) are not toxic to cardiomyocytes and might impact mitochondrial function, enabling us to move forward with additional testing of these countermeasures in EHTs. The impact of these findings is that they provide strong corroborating evidence for mitochondrial injury in human cell lines and EHTs that we previously observed in mouse and rat heart tissues following protracted exposure to low-dose rate neutron irradiation in vivo. This means that we can extrapolate the findings from our rodent models of space radiation-induced cardiac dysfunction to humans, and further validate candidate countermeasures identified in EHTs and in rodent models. Over the upcoming year, we will irradiate EHTs with low-dose rate neutrons using the new D-T neutron irradiator recently installed at Colorado State University (CSU) to evaluate high LET radiation effects on mitochondrial function and contractile function, search for biomarkers of neutron-irradiation damage in the EHT secretome, and expand our testing of countermeasures against radiation injury mediated by oxidative stress and DNA damage using treatments such as aspirin, MitoTEMPO, and FASTmers targeting regulators of NRF2.
Bibliography Type:	Description: (Last Updated: 09/27/2023)
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