Fiscal Year:	FY 2022	**Task Last Updated:**	FY 10/12/2022
PI Name:	Gerecht, Sharon Ph.D.		
Project Title:	Using Human Stem-Cell Derived Vascular, Neural, and Cardiac 3D Tissues to Determine Countermeasures for Radiation		
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:	21218	**Congressional District:**	7
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:	10/01/2020	**End Date:**	08/31/2024
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	3	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	1	**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 08/31/2024 per E. Urquieta/TRISH (Ed., 12/22/23). NOTE: End date changed to 04/30/2024 per E. Urquieta/TRISH (Ed., 3/21/23). Original end date was 09/30/2023.		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Boehler, Kenneth Ph.D. (Johns Hopkins University) Chancellor, Jeffrey Ph.D. (Louisiana State University) Hienz, Robert Ph.D. (Johns Hopkins University) Kim, Deok-Ho Ph.D. (Johns Hopkins University) Lee, Gabsang Ph.D. (Johns Hopkins University) Shelhamer, Mark Sc.D. (Johns Hopkins Medical School) Xu, Jinchong Ph.D. (Johns Hopkins University) Tung, Leslie Ph.D. (Johns Hopkins University) Spangler, Jamie Ph.D. (Johns Hopkins University) Mallick, Parag Ph.D. (Stanford University)		

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Performance Goal No.:	
Performance Goal Text:	
Task Description:	In this study, a skilled team with diverse expertise will examine 3D human tissue models for their response to radiation, with an eye to the development of countermeasures. Cardiovascular and neuronal degeneration are established risks of exposure to deep-space radiation (galactic cosmic rays or "GCR"). Inflammation and oxidative damage are dominant mechanisms, which are being addressed with appropriate pharmaceuticals or supplements. There are, however, various forms of protein modification, including oxidation, reduction, and changes in expression. These have been demonstrated at relatively high dosages with terrestrial radiation sources, providing an impetus for further investigation into damage mechanisms that impact protein structure and function. Thus, we propose here a broad assay for altered protein expression and changes in protein function, which may lead to genetic and proteomic interventions that target the most-affected sites. This is complemented with an investigation of the signaling pathways that might propagate these effects. We analyze responses of three human tissue models to low-dose protracted GCR simulations, and identify and develop countermeasures using optogenetics and molecular antagonists. Human tissue models include vascular, cerebrovascular, and cardiac. These are 3D constructs generated from human pluripotent stem cells (hPSCs) and are well characterized. Radiation exposures are in alignment with NASA guidelines. In a slight departure, we make use of a newly developed method to modify the standard GCR beam at NASA Space Radiation Laboratory (NSRL) in order to provide a GCR spectrum that better emulates one inside a spacecraft. This alleviates some of the concerns with the existing radiation sources, and provides a more direct transfer of our results to the actual spaceflight situation. The project is organized into three specific aims. First, we determine the effect of radiation exposure on cell viability and cell cycle, tissue integrity and functionality, and the activation of oxidative stress and high mobility group box 1 (HMGB1) pathways. This will validate the usefulness of our biological models, and radiation exposures, for the subsequent investigation of countermeasures. Second, we use an integrative systems approach to identify therapeutic (countermeasure) targets to mitigate radiation damage. This is accomplished with large-scale quantitative proteomics, multi-data fusion and network analysis, and conformational inhibition tests. Ultimately, in aim three, we develop and test countermeasures based on optogenetics and protein antagonists, to activate or inhibit pathways impacted by radiation. The results of this project will help to determine if complex human models can serve as an effective testbed for the effects of space radiation on intact humans, and will identify and assess possible countermeasures to these effects.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The results of this project help to determine if complex human models can serve as a practical testbed for the effects of space radiation on intact humans and identify and assess possible countermeasures to these effects.
Task Progress:	In this study a skilled team with diverse expertise will examine 3D human tissue models for their response to radiation, with an eye to the development of countermeasures. Cardiovascular and neuronal degeneration are established risks of exposure to deep-space radiation GCRs. Inflammation and oxidative damage are dominant mechanisms, which are being addressed with appropriate pharmaceuticals or supplements. There are, however, various forms of protein modification including oxidation, reduction, and changes in expression. These have been demonstrated at relatively high dosages with terrestrial radiation sources, providing an impetus for further investigation into damage mechanisms that impact protein structure and function. Thus, we propose a broad assay for altered protein expression and changes in protein function, which may lead to genetic and proteomic interventions targeting the most affected sites. This is complemented with an investigation of the signaling pathways that might propagate these effects. We analyze responses of three human tissue models to low-dose protracted GCR simulations and identify and develop countermeasures using optogenetics and molecular antagonists. Human tissue models include vascular, cerebrovascular, and cardiac. These are 3D constructs generated from hiPSCs and are well characterized. The specific aims are: (1) Characterizing responses of 3D models of human vasculature, neurovascular, and cardiac tissues to exposure to space radiation; (2) An integrative systems-medicine approach to identifying therapeutic targets for minimizing space-radiation-induced damage; and (3) Developing and testing countermeasures using optogenetics and protein antagonist therapies to protect human tissue from radiation damage. Preliminary findings following the first year of the project indicate that simulated GCR potentially poses a significant risk to vascular, heart, and neurovascular health. Following GCR exposure experiments, we also note the need to adjust our 3D tissue models to continue with the proposed experiments. Computational network models of drug-gene interactions that integrate across numerous data sources were created. Finessing our proteomic cell extraction protocols and workflow to fit the 3D tissue models is in progress. Countermeasure development continues with the establishment of the Opto-fibroblast growth factor receptor (Opto-FGFR) hiPSC line and engineering an antagonist to target HMGB1. Our findings thus far do not alter our original hypothesis or the objective and aims as originally proposed. Ongoing modifications to our technologies and protocols would support the proposed experimental plan and will continue into next year. We will continue to characterize responses of the human complex model for space radiation, integrate advanced computational techniques for multi-scale modeling proteome, and begin testing countermeasures. ---------- Additional progress notes from PI (Ed., 10/12/22) • While still within the preliminary stages of the research project, we have putatively identified key consequences of simulated GCR exposure on our 3D human tissues. • Improvements to our model systems are enabling us to perform in depth analyses of radiation impact. • Key modifications were made to identify protocols for cell extraction from the 3D human model systems for downstream molecular analysis. • Refinements of proteomics workflows for operating on small amounts of material were made. • Computational network models of drug-gene interactions that integrate across

	numerous data sources were created. • Using optogenetics we began to develop a potential countermeasure to GCR in the human iPSC line. • Ongoing countermeasure development work is designing a novel anti-inflammatory protein that promises to have utility in preventing radiation damage. • Our successful presentation of the HMGB1 box A domain on the yeast surface display platform empowers new directions in engineering immunomodulatory proteins as targeted drugs. • Monte Carlo simulations of the GCR blocker enabling us to determine the experimental exposures to more closely reflect the field that would be incurred by these cells at the depth in tissues during spaceflight.
Bibliography Type:	Description: (Last Updated: 03/19/2024)
Articles in Peer-reviewed Journals	Macklin BL, Lin YY, Emmerich K, Wisniewski E, Polster BM, Konstantopoulos K, Mumm JS, Gerecht S. "Intrinsic epigenetic control of angiogenesis in induced pluripotent stem cell-derived endothelium regulates vascular regeneration." npj Regen Med. 2022 May 12;7:28. https://pubmed.ncbi.nlm.nih.gov/35551465 ; PubMed PMID: 35551465; PubMed Central PMCID: PMC9098630 , May-2022
Articles in Peer-reviewed Journals	Schnellmann R, Ntekoumes D, Choudhury MI, Sun S, Wei Z, Gerecht S. "Stiffening matrix induces age-mediated microvascular phenotype through increased cell contractility and destabilization of adherens junctions." Adv Sci (Weinh). 2022 Aug;e2201483. https://pubmed.ncbi.nlm.nih.gov/35657074 ; PubMed PMID: 35657074; PubMed Central PMCID: PMC9353494 , Aug-2022
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Awards	Gerecht, S. "Fellow of the American Association for the advancement of Science (AAAS), January 2021." Jan-2021
Awards	Gerecht, S. "Member of the National Academy of Inventors (NAI), December 2020." Dec-2020
Awards	Yarbrough D. "National Science Foundation (NSF) Graduate Research Fellowship Program (GRFP), June 2022." Jun-2022
Awards	Mair D. "Young Investigator award from the MPS World Summit (June 2022), AHA predoctoral fellowship (April 2022), Tom Scott Award from the American Society for Gravitational and Space Research (February 2022)." Jun-2022
Awards	Sagunas P. "Whiting School of Engineering Trainee Award, May 2022." May-2022