Fiscal Year:	FY 2022	**Task Last Updated:**	FY 07/13/2022
PI Name:	Blutt, Sarah Ph.D.		
Project Title:	Use of Microbial Based Countermeasures to Mitigate Radiation Induced Intestinal Damage		
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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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:**	09/30/2023
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	2	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 9/30/2023 per TRISH (Ed., 8/4/22)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Britton, Robert Ph.D. (Baylor College of Medicine) Coarfa, Cristian Ph.D. (Baylor College of Medicine) Estes, Mary Ph.D. (Baylor College of Medicine) Grosshans, David M.D., Ph.D. (The University of Texas M.D. Anderson Cancer Center) Taniguchi, Cullen M.D., Ph.D. (The University of Texas M.D. Anderson Cancer Center)		
Grant/Contract No.:	NNX16AO69A-RAD0101		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Very little is known about how exposure to space radiation might affect gastrointestinal health and function. The high turnover rate of the intestinal stem cell (ISC) predicts that the small intestine will be vulnerable to the effects of radiation exposure associated with long duration space flight. However, there is much that is unknown about the response of the human ISC to space radiation due to the lack of in vitro and in vivo mechanistic data and systems that model the complex biology and physiology of the human small intestine. Human intestinal organoid (HIOs) cultures provide a new model system in which (1) the impacts of simulated space radiation on the ISC can be examined, (2) biomarkers of small intestinal damage and repair following radiation exposure can be identified, and (3) countermeasures to the damage can be explored. One potential countermeasure for intestinal damage is the gastrointestinal microbiome. A postulated function of the microbiome is to regulate intestinal epithelial homeostasis and participate in epithelial repair. However, neither the specific microbial communities or their factors that are capable of inducing these effects nor the epithelial cellular pathways induced have been elucidated. We have treated HIOs with conditioned media obtained from complex commensal communities derived from human stool and found that factors produced by specific communities stimulate proliferative and stem cell marker expression suggesting that the microbiome may be a putative countermeasure for space radiation induced damage of the small intestine. The results from this study will provide direct insights into the effects of simulated space radiation on the small intestinal epithelium and elucidate microbial countermeasures that facilitate epithelial renewal.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	• Leveraging cutting edge technology of human organoid intestinal model that recapitulates physiology of human intestine in vitro to study human spaceflight risk. • Promising new approach to translate use of microbiome to mitigate intestinal damage into appreciable health outcomes for astronauts during spaceflight.
Task Progress:	Update from the Translational Research Institute for Space Health (TRISH) and the Principal Investigator (PI): In the last year, we have generated two large transcriptomic datasets from HIOs exposed to either gamma or proton source radiation. We are using these datasets to establish a unique set of biomarkers that associate with proton induced effects on the human intestinal epithelium including identifying individual cell type specific biomarkers using single cell transcriptomics. We are validating these datasets by comparison to publicly available datasets. Using these comparisons, we have identified that proton exposure of HIOs results in a transcriptional profile that has many similarities to irritable bowel syndrome (IBS) with diarrhea symptoms. Using single cell transcriptomic analysis, we see certain populations of cells including secretory cells are particularly vulnerable to proton radiation; yet the stem cells appear to be responding by upregulating cell cycle genes and pathways. These results provide support for targeting or protecting the intestinal stem cell through mitigation via microbial derived factors. In the coming year, we plan to validate our biomarker datasets using more conventional laboratory-based approaches to complement our bioinformatic data. We have completed our bioengineering of L. Reuteri, creating several modified bacterial organisms that are able to express factors that enhance ISC proliferation, an initial step required for regeneration and repair of the intestinal epithelium. We plan on extending this testing to determine the capacity to prevent or reverse the radiation damage induced in the HIOs. (Ed., 1/19/23) Very little is known about how exposure to space radiation might affect gastrointestinal health and function. The high turnover rate of the intestinal stem cell (ISC) predicts that the small intestine will be vulnerable to the effects of radiation exposure associated with long duration spaceflight. The aims of our project are to utilize the human intestinal organoid (HIO) model to (1) establish the impacts of simulated space radiation on the ISC as reflected in a unique set of biomarkers of damage and repair, and (2), assess the ability of microbial based countermeasures to reverse the radiation induced damage. In the last year, we have made several key findings. We have examined the response of the organoids to different doses and linear energy transfer (LET) of proton radiation and compared the response to an equivalent dose of gamma radiation. We have examined the response of the organoids to treatment with generally regarded a safe (GRAS) bacterial organisms and have used genetic modification to enhance those strains that have positive effects on organoid growth. Both radiation studies and microbial countermeasure development studies have been enhanced by the use of publicly available datasets derived from intestinal exposure to radiation and stem cell recovery and regeneration. The results from this study directly address our study objectives and will provide direct insights into the effects of simulated space radiation on the small intestinal epithelium and elucidate microbial countermeasures that facilitate epithelial renewal. In the coming year, we will continue to explore the response of the organoids to radiation by using both single cell and bulk transcriptomic analysis prior to and following radiation exposure with the goal of establishing biomarkers of intestinal damage. Our bioinformatics analysis will be used to guide the establishment of these biomarkers. We will begin to test the genetically modified organisms for the capacity to prevent or reverse the radiation-induced damage in the organoids. These studies will facilitate the exploration of the microbiome as a basis for novel, safe, and cost-effective countermeasure to manage intestinal damage following radiation exposure.
Bibliography Type:	Description: (Last Updated: 01/11/2023)
Articles in Peer-reviewed Journals	Bokhari RS, Beheshti A, Blutt SE, Bowles DE, Brenner D, Britton R, Bronk L, Cao X, Chatterjee A, Clay DE, Courtney C, Fox DT, Gaber MW, Gerecht S, Grabham P, Grosshans D, Guan F, Jezuit EA, Kirsch DG, Liu Z, Maletic-Savatic M, Miller KM, Montague RA, Nagpal P, Osenberg S, Parkitny L, Pierce NA, Porada C, Rosenberg SM, Sargunas P, Sharma S, Spangler J, Tavakol DN, Thomas D, Vunjak-Novakovic G, Wang C, Whitcomb L, Young DW, Donoviel D. "Looking on the horizon; potential and unique approaches to developing radiation countermeasures for deep space travel." Life Sci Space Res (Amst). 2022 Nov;35:105-12. https://doi.org/10.1016/j.lssr.2022.08.003 . Epub 2022 Aug 7. PMID: 36336356 , Nov-2022
Awards	Sawyer F. "Position on T32 Clinical Translation Research-Full Salary Support." Jul-2022
Awards	Blutt S. "American Journal of Physiology-Gastrointestinal (AJPGI) distinction in scholarship for article." Sep-2022
Awards	Blutt S. "Video Abstract of work highlighted on American Journal of Physiology-Gastrointestinal (AJPGI) home webpage." Sep-2021