Fiscal Year:	FY 2020	**Task Last Updated:**	FY 05/15/2020
PI Name:	Rosenberg, Susan Ph.D.		
Project Title:	Discovery of Human Radiation-protection Genes and Pathways		
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		
PI Email:	smr@bcm.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	713-798-6924
Organization Name:	Baylor College of Medicine		
PI Address 1:	1 Baylor Plz		
PI Address 2:	Rm S809A		
PI Web Page:			
City:	Houston	**State:**	TX
Zip Code:	77030-3411	**Congressional District:**	9
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2017 HERO NNJ16ZSA001N-TRIRT. Appendix C: Translational Research Institute for Space Health (TRISH) Research Topics
Start Date:	10/01/2017	**End Date:**	09/30/2021
No. of Post Docs:	2	**No. of PhD Degrees:**	2
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	0	**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 9/30/2021 per TRISH (Ed., 5/27/20)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Miller, Kyle Ph.D. (Baylor College of Medicine)		
Grant/Contract No.:	NNX16AO69A-T0109		
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Performance Goal Text:			

Task Description:	Individuals in high-radiation environments, including space, suffer DNA damage, which increases their susceptibility to cancer, among other diseases. The levels of DNA damage accumulated in cells can be used to measure the extent to which cells succumb to, or alternatively resist, the deleterious consequences of radiation. This project leverages the only known collection of genes that confer lower-than-normal levels of spontaneous DNA damage to cells to identify proteins that confer resistance to exogenous proton-beam (space-relevant) radiation. Unique resource: We discovered 231 Escherichia coli (bacterial) genes that alter levels of DNA damage in cells when overproduced—208 that increase and 23 that decrease DNA damage, the latter of interest to radiation resistance. The human-gene relatives of the bacterial damage-up genes also increased DNA damage when overproduced in human cells, and are highly significantly overrepresented among known cancer-driving genes. These data demonstrate the relevance and power of conserved bacterial genes for discovery of important human biology of DNA damage. Plan: We will explore the 23 E. coli DNA damage-down genes and their human homologs and analogs for their ability, when overproduced, to protect cells from exogenously applied proton-induced DNA damage. We will identify—(1) which E. coli genes confer resistance to proton-induced DNA damage; (2) what kinds of DNA damage they reduce; (3) which of their human-gene relatives confer resistance to proton-mediated DNA damage when overproduced, and guided by the bacterial results, test hypotheses for how they do so. Deliverables: Identities of bacterial and human proteins that protect cells from DNA damage induced by proton beams, a proxy for protection from radiation generally, and some of the mechanisms by which they do so. The human proteins and pathways of radiation resistance, when understood, can be considered as potential targets for, or models for design of, drugs for protection from radiation.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	We aim to identify target proteins to reduce endogenous DNA damage when overproduced, the pharmacological manipulation of which could potentially promote enhanced radiation resistance to astronauts in space, and may also prevent cancer, age-related neurodegenerative and other diseases.
Task Progress:	[Ed. note May 2020: Report submitted by TRISH to Task Book in March 2020; covers reporting as of September 2019.] Overview: This project leverages our discovery of a set of conserved bacterial proteins that, when overproduced, confer reduced cellular levels of endogenous DNA damage. We use these for prediction and potential discovery of similar human proteins that may promote resistance to exogenous DNA-damaging agents including space-relevant radiation. The project goals are to discover which of 23 Escherichia coli (bacterial) endogenous DNA Damage-Suppressing Proteins (DDSPs) can reduce DNA damage from exogenous sources, some of the mechanisms by which they do so, and which of their human counterparts may do this. The ultimate goal is to understand whether pharmacologically increased production of some/any of the human candidate proteins might protect astronauts from radiation in space, and also potentially extend healthy life-span and prevent cancer in people on Earth. We have made significant progress on the two aims: Aim 1. Discovery of E. coli DNA damage-down proteins that protect bacteria from exogenous DNA damage when overproduced. Aim 2. Discovery of human homologs, analogs, and pathways that protect human cells from exogenous DNA damage when overproduced. Key findings 1. Dose-response curves were generated and used to determine appropriate experimental conditions for treatment of E. coli cells with the exogenous gamma rays. We have demonstrated two E. coli radiation-protection proteins (RPPs) that protect cells from DNA damage caused by either IR when overproduced. 2. At least two E. coli DDSPs confer better survival after IR. 3. An E. coli DDSP overproduction reduces DNA damage while improving cell survival-a bacterial model for human general stress response pathways. 4. At least three E. coli DDSPs reduce spontaneous mutation rates when overproduced. 5. Cloning completed. We have cloned all possible full-length green fluorescent protein (GFP) fusions (>70) of human candidate DDSP genes, determined their subcellular localization patterns, and re-cloned mis-localized N-terminal GFP fusion as C-terminal GFP fusions. 6. An initial screen of correlated localized 79 human homologs (proteins of similar aminoacid sequence) and analogs of the bacterial DDSPs (proteins that function similarly to the E. coli proteins but no sequence identity) indicate that many show reduced endogenous DNA-damage levels. Further careful confirmations validated at least 8 out of 11 initial hits. 7. A few human RPPs were discovered; more remain to be tested. Impact 1. We will further optimize conditions with gamma rays. This is a critical prerequisite to identify all of the E. coli RPPs. 2. Our initial hypothesis that DDSPs might protect cells from both endogenous and exogenous DNA damage has been supported in E. coli and human cells. This validates the basis of the project. 3. Human GFP fusions cloning have been completed. 4. Determination of conditions for experiments using X-rays in one human cell line is complete, and has been initiated for another human cell line. This lets the project proceed. 5. Preliminary data, which still require repetition and validation, suggest that many human candidate proteins predicted by the E. coli network may reduce endogenous DNA damage levels (be hDDSPs) when overproduced, potentially paving the way to discovery of radiation-protection proteins among them. Much work remains to validate these, but the first

	results are promising. 6. We discovered at least 8 genuine hDDSPs that reduce endogenous DNA damage in human cells, yielding candidates for human RPP testing. 7. Overproduction of two demonstrated hDDSP protect human cells from gamma rays so they are human RPPs. These proteins will be the first to be tested in the proton beams and will be prioritized as drug targets.
Bibliography Type:	Description: (Last Updated: 03/13/2025)