Fiscal Year:	FY 2018	**Task Last Updated:**	FY 02/22/2018
PI Name:	Fox, Donald Ph.D.		
Project Title:	Mining Biology's Extremes for New Space Radiation Resistance Strategies		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
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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:**	2017 HERO NNJ16ZSA001N-TRIRT. Appendix C: Translational Research Institute for Space Health (TRISH) Research Topics
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No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
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Key Personnel Changes/Previous PI:			
COI Name (Institution):	Kirsch, David M.D., Ph.D. (Duke University)		
Grant/Contract No.:	NNX16AO69A-T0108		
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Using powerful genetic screening in Drosophila and follow-up work in mice, we will identify unique genes and gene expression that enhance space radiation tolerance in vivo. Our approach will identify new, organism-relevant strategies to provide space radiation resistance.
1-Specific Aims

Aim1- A targeted Drosophila screen of candidate factors from Tardigrades (Ramazzottius varieornatus) that enhance radiation resistance.

Aim2- An unbiased screen for genes that enhance radiation resistance in the Drosophila hindgut.

Task Description:	2-Relevance The purpose of this proposal is to uncover new understanding of how a species withstands space-relevant radiation exposure, using validation and safety efficacy studies in model organisms. Drosophila is specifically mentioned, and we have expertise in study of Drosophila radiation resistance mechanisms (Bretscher and Fox 2016, Dev Cell). We will perform genetic manipulation in vivo in flies, targeting potential Tardigrade resilience mechanisms. Finally, we discuss follow-up work in rodents, which we are well-equipped to do, as Duke co-investigator Dr. Kirsch has prior NASA-funded experience in studying space radiation effects in mice at Brookhaven NASA Space Radiation Laboratory (NSRL). 3-Approach Aim1- We will generate novel Drosophila strains expressing candidate Tardigrade genes, and assay their effects on resistance to both high charge and energy (HZE) particles (56Fe), and as a comparison, X-ray irradiation. Tardigrades have recently shown promise for finding factors that enhance radiation tolerance (Hashimoto et al., Nat. Comm. 2016). Genome data for this radiation-resistant organism is now available. From our collaborators Bob Goldstein, we will obtain animals for cDNA generation. We will generate up to 165 unique fly lines, each expressing a Tardigrade gene that, relative to Drosophila or humans, is is unique (low homology) and/or induced by radiation. Flies will then be subjected to HZE particles at NSRL or X-irradiation at Duke, and monitored for long-term survival, multi-generational fecundity, and will be sequenced at distinct generations to quantify radiation-induced mutations. Genes with promising enhanced radiation resistance will be pursued further in transgenic mice subjected to similar tests as in flies. Aim2- Relative to candidate screens (Aim1), un-biased fly screens are more applicable to genome-wide study. The Fox laboratory recently identified a Drosophila cell type (hindgut papillar cells) that is highly resistant to X-irradiation, and used a simple in vivo candidate screen to find genes required for the heightened radiation resistance. Expanding on this successful strategy, we will screen 1/5 of the entire genome through EMS mutagenesis. Mutant strains will be assayed for DNA damage resistance in hindgut papillar cells. Interesting mutants will be sequenced to find causative genes. We will then generate transgenic flies expressing genes that mediate radiation resistance throughout the fly, and perform tests of HZE particle and X-irradiation resistance, including long-term organismal assays and follow-up mouse experiments as in Aim1. 4-Impact and 5-Rationale for mitigating space exploration risks Space radiation poses a significant threat to astronaut health, and novel approaches are needed to limit space radiation damage. Drosophila and mice provide convenient, in vivo-relevant screening platforms, and effects on organism health, such as fecundity, can be scored. Understanding mechanisms that prevent space radiation damage in model organisms may uncover new space radiation resistance strategies to be targeted in humans. Such strategies would accelerate the pace of space discovery while protecting astronaut lives. Bretscher, H. S. & Fox, D. T. Proliferation of Double-Strand Break-Resistant Polyploid Cells Requires Drosophila FANCD2. Dev Cell 37, 444–457 (2016). Hashimoto, T. et al. Extremotolerant tardigrade genome and improved radiotolerance of human cultured cells by tardigrade -unique protein. Nat Comms 7, 12808 (2016).
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	New project for FY2018.
Bibliography Type:	Description: (Last Updated: 09/04/2023)