Fiscal Year:	FY 2021	**Task Last Updated:**	FY 07/22/2021
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		
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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PI Organization Type:	UNIVERSITY	**Phone:**	919-613-8756
Organization Name:	Duke University Medical Center		
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City:	Durham	**State:**	NC
Zip Code:	27710	**Congressional District:**	1
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:**	12/31/2020
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	2
No. of Bachelor's Candidates:	4	**Monitoring Center:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/31/2020 per TRISH (Ed., 6/17/2020)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Kirsch, David M.D., Ph.D. (Duke University Medical Center)		
Grant/Contract No.:	NNX16AO69A-T0108		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The purpose of this solicitation 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). As outlined in the solicitation, we will perform genetic manipulation in vivo in flies, targeting potential Tardigrade resilience mechanisms. Finally, the solicitation discusses 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). Reference: Bretscher, H. S. & Fox, D. T. Proliferation of double-strand break-resistant polyploid cells requires Drosophila FANCD2. Dev Cell 37, 444–457 (2016).
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	These transgenic flies described in aim1 of our research report represent a new resource for the study of Tardigrade gene products and their potential impact on the biology of extreme environmental stress resistance, including resistance to radiation. We have identified multiple tardigrade-unique genes as important tools for countermeasure development. Our aim2 findings suggest that expression of the CRL4/CDT2 complex can also play an important role in radioprotection.
Task Progress:	1. Original project aims/objectives 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. 2. Key findings Aim 1- After year 3, we completed our generation of 98 transgenic fly lines to test candidate radioprotector Tardigrade genes. We have now conducted replicated tests of survival after X-ray irradiation (low-linear energy transfer (LET)), as well as after 56Fe irradiation (high LET) for over 70 lines. From these studies, a recurrent theme is that specific Tardigrade superoxide dismutase (SOD) genes are promising radioprotectors. Most excitingly, we found one tardigrade SOD that acts as a radioprotector for both high and low LET radiation, and is superior to its fly counterpart in terms of radioprotection in a fly. Further, we have preliminary evidence that the same top SOD radioprotector found in our fly studies also acts as a novel and potent radioprotector in human cells. Aim2- After year 3, we screened ~1300 lethal mutant stocks for our proposed unbiased screen. This resulted in the identification of the CRL4/CDT2 complex as an important regulator of radioprotection in fly papillar cells. 3. Impact of key findings on original objectives Both aims were successful in identifying radioprotectors in flies. A second goal of both aims was to carry these studies forward into mammalian cells. To this end, we have generated cell lines for top-performing radioprotectors from Aim1, and irradiated these lines using high LET radiation (56Fe) at Brookhaven NASA Space Radiation Laboratory (NSRL). Results are not available yet at the time of this progress report, but we are close to achieving the stated goal of the original proposal. 4. Plan for the coming year Our funding for this project has ended. Our goal is to finalize our studies and publish them in 2021. Our current studies in mammalian cells will be valuable in terms of seeking additional NASA support and for further development of our findings into countermeasures that could be made available to astronauts in the future.
Bibliography Type:	Description: (Last Updated: 09/04/2023)
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." 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 ; PMID: 36336356 , Aug-2022