Fiscal Year:	FY 2021	**Task Last Updated:**	FY 11/19/2021
PI Name:	Brenner, David Ph.D.		
Project Title:	Physical and Biological Modulators of Space Radiation Carcinogenesis: Mechanistically- Based Model Development for Space Radiation Risk Assessment		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline-- Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cancer**:Risk of Radiation Carcinogenesis		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	10032	**Congressional District:**	13
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	Directed Research
Start Date:	08/26/2016	**End Date:**	08/25/2021
No. of Post Docs:	1	**No. of PhD Degrees:**	
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:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 8/25/2021 per NSSC information (Ed., 4/30/21) NOTE: End date changed to 2/25/2021 per NSSC information (Ed., 9/3/20)		
Key Personnel Changes/Previous PI:	n/a		
COI Name (Institution):	Hei, Tom Ph.D. (Columbia University Center for Radiological Research)		
Grant/Contract No.:	NNX16AR81A		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The main goal of the current project is state of the art mechanistically-motivated modeling of experimental data from the NASA Specialized Center of Research (NSCOR) programs and the published literature. The ultimate purpose is to generate reliable estimates of heavy ion related cancer risks and uncertainties in astronauts on lengthy space exploration missions. This task consists of four major components: The first component involves developing mechanistically-motivated mathematical models for heavy ion-induced carcinogenesis. It includes both targeted effects (TE), caused by DNA damage resulting from traversal of cells by ionizing tracks, and non-targeted effects (NTE), caused by radiation-induced perturbation of molecular signaling pathways between traversed and non-traversed cells. The second component involves estimating site-specific and consensus dose response functions for heavy ions produced by model-based analysis of NSCOR experimental data. The third component involves generating realistic uncertainty estimates for the functions from component two. Finally, in the fourth component, we will compare our results and uncertainties with current risk estimates and uncertainties from NASA. To estimate heavy ion-induced cancer risks in astronauts engaged in long-distance space exploration such as a flight to Mars, we developed and are refining a mechanistically-motivated mathematical model of space radiation induced carcinogenesis. Our model (Shuryak et al., 2017) combines TE and NTE components. The TE component over the dose range of interest for space missions is reasonably described by a linear dependence. In contrast, the NTE component for heavy ions tends to be non-linear with a concave shape. The recently updated mouse tumorigenesis data from our collaborators at Georgetown University show that not only overdispersion relative to the Poisson distribution (where variance/mean > 1), but also underdispersion (variance/mean < 1) are encountered, depending on radiation type and dose. Consequently, we generated a new detailed error distribution approach for the variability of tumor count data based on the weighted negative binomial (WNB) distribution. The motivation for using this more complex model is to reduce the errors on model-based radiation quality assessments and risk estimates by improved handling of the data variances. Reference: Shuryak, I., Fornace, A.J., Datta, K., Suman, S., Kumar, S., Sachs, R.K., Brenner, D.J., 2017. Scaling Human Cancer Risks from Low LET to High LET when Dose-Effect Relationships are Complex. Radiat. Res. 187, 476–482.
Rationale for HRP Directed Research:	This research is directed because it contains highly constrained research, which requires focused and constrained data gathering and analysis that is more appropriately obtained through a non-competitive proposal. The timing of this work supports current efforts by the Risk Assessment project to quantify uncertainties due to radiation quality factors and use of the dose and dose-rate effectiveness factor (DDREF). Work is highly synergistic with on-going work in the Fornace NSCOR as well as in assessing tissue-specific quality factors and DDREF specific to GI (gastrointestinal) cancers. The study will integrate data from multiple NSCORs (NASA Specialized Centers of Research).
Research Impact/Earth Benefits:	Cancer is the second leading cause of death in the United States, exceeded only by heart disease (https://). It accounts for one of every four deaths in the United States. More than 1.8 million new cancer cases and over 606,500 cancer-related deaths are predicted to occur in the U.S. in 2020 (https://). Considering this high frequency and lethality of cancer, even a small increase by space radiation would have a major impact on planning and design of future interplanetary manned space missions. Accurate estimation of space radiation-related cancer risks is, therefore, very important for NASA mission planning. Mathematical models of radiation carcinogenesis are important tools in this task.
Task Progress:	The main results of this study were the best-fit unfolded functions for the TE and the NTE metrics. The functions for the TE and the NTE metrics both peak at lineal energies between 50 and 100 keV/μm, but their overall shapes are clearly different, particularly at intermediate lineal energy values. As an example of potential utility of this approach, we applied the best-fit functions for TE and NTE to calculated microdosimetric lineal energy deposition distributions for the space environment and for the surface of Mars. The results predicted TE and the NTE low-dose metrics for the space environment and for the Mars surface. The metrics were somewhat higher for the space environment than for the Mars surface because the space environment spectrum contained a larger contribution of high lineal energies (Northum et al., 2015). Of interest is that the low-dose metrics for NTE were 2-3 fold higher than those for TE. [Ed. Note. Reference: Northum, J.D., Guetersloh, S.B., Braby, L.A., Ford, J.R., 2015. Simulated response of a tissue-equivalent proportional counter on the surface of Mars. Health Phys. 109, 284–295. doi:10.1097/HP.0000000000000335 .]
Bibliography Type:	Description: (Last Updated: 06/28/2023)
Articles in Peer-reviewed Journals	Shuryak I, Brenner DJ. "Review of quantitative mechanistic models of radiation-induced non-targeted effects (NTE)." Radiat Prot Dosimetry. 2020 Nov;192(2):235-52. https://doi.org/10.1093/rpd/ncaa207 ; PMID: 33395702; PMCID: PMC7840098 , Nov-2020
Articles in Peer-reviewed Journals	Shuryak I, Brenner DJ. "Quantitative modeling of multigenerational effects of chronic ionizing radiation using targeted and nontargeted effects." Sci Rep. 2021 Feb 26;11(1):4776. https://doi.org/10.1038/s41598-021-84156-2 ; PMID: 33637848; PMCID: PMC7910614 , Feb-2021
Articles in Peer-reviewed Journals	Shuryak I, Brenner DJ, Blattnig SR, Shukitt-Hale B, Rabin BM. "Modeling space radiation induced cognitive dysfunction using targeted and non-targeted effects." Sci Rep. 2021 Apr 23;11(1):8845. https://doi.org/10.1038/s41598-021-88486-z ; PMID: 33893378; PMCID: PMC8065206 , Apr-2021
Articles in Peer-reviewed Journals	Shuryak I, Sachs RK, Brenner DJ. "Quantitative modeling of carcinogenesis induced by single beams or mixtures of space radiations using targeted and non-targeted effects." Sci Rep. 2021 Dec 6;11(1):23467. https://doi.org/10.1038/s41598-021-02883-y ; PMID: 34873209; PMCID: PMC8648899 , Dec-2021

Articles in Peer-reviewed Journals	Shuryak I, Slaba TC, Plante I, Poignant F, Blattnig SR, Brenner DJ. "A practical approach for continuous in situ characterization of radiation quality factors in space." Sci Rep. 2022 Jan 27;12(1):1453. https://doi.org/10.1038/s41598-022-04937-1 ; PMID: 35087104; PMCID: PMC8795169 , Jan-2022