Fiscal Year:	FY 2019	**Task Last Updated:**	FY 06/25/2019
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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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	Directed Research
Start Date:	08/26/2016	**End Date:**	08/25/2020
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
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
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:	This project is designed to use state-of-the-art mechanistic modeling of the experimental data from NASA Specialized Center of Research (NSCOR) programs and other available data as a basis to generate HZE (high energy particle) related cancer risk and uncertainty estimates in humans. There are four components: First, development of practical mechanistically motivated models, emphasizing the significance of individual radiation sensitivity. Second, based on model-based analysis of our and other NSCOR experimental data, estimate site-specific and consensus quality functions for HZE ions. Third, generate realistic uncertainty estimates for these estimates. Finally, our results and uncertainties will be critically compared with the current NASA projections and uncertainties. In order to answer the critical question of how to reliably estimate heavy ion-induced cancer risks in astronauts embarking on long-distance space exploration missions such as a flight to Mars, we are developing a mechanistically-motivated mathematical model that can predict radiogenic carcinogenesis as function of dose and dose		

	rate using both targeted effect (TE) and non-targeted effect (NTE) contributions. Importantly, such models are needed to predict low dose rate risks based on data at higher dose rates because the very low heavy ion dose rates relevant for space missions are difficult to achieve in terrestrial experiments. Our goal is to calibrate the carcinogenesis model using available human and animal data and to generate scaling factors such as the recently proposed radiation effects ratio (RER), which compares carcinogenic effectiveness of heavy ions and gamma rays at the dose of interest. The scaling factors would then be used to estimate human heavy ion-induced cancer risks, based on human gamma-ray-induced risks. An important focus of our work is generation of realistic uncertainties for model parameters and predictions, which ultimately translate into realistic uncertainties on astronaut risk estimates.
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 (gastronintestinal) 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 1.7 million new cancer cases and over 600,000 cancer-related deaths are predicted to occur in the US in 2018 (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.
Task Progress:	Galactic cosmic ray (GCR) radiation includes multiple types of heavy ions (with Z>=2) with high linear energy transfer (LET). When such ions traverse biological materials, such as the human body, they produce densely-ionizing "Core" tracks surrounded by sparsely-ionizing delta ray paths. These multi-component energy deposition patterns result in broad spectra of damage on a molecular scale, from very severe clustered lesions (e.g., complex and difficult to repair DNA double strand breaks) to diffuse oxidative damage (e.g., due to reactive oxygen species from water radiolysis). Incorrectly repaired radiation-induced damage can become a precursor to carcinogenesis, and the risk of this process from GCR exposures received during lengthy space missions is a major concern for planning long-distance human-piloted space exploration missions like an expedition to Mars. Because the complex space radiation mixtures (consisting of protons and various types of heavy ions, as well as photons and neutrons) are difficult to recreate experimentally on Earth, mechanistically-motivated mathematical models represent valuable tools that help to enhance the interpretation of terrestrial experiments, generate quantitative predictions of risks from space exposures, and scale risk estimates from experimental animals to humans. We developed and tested such models on several data sets [7-10]. Here we apply our modeling approach to new data obtained by our collaborators from Georgetown University at the NASA Space Radiation Laboratory (NSRL). Model-based analysis of these expanded data sets on animal carcinogenesis, which cover a broad space-relevant LET range of 2-148 keV/µm, allows a more thorough investigation of how TE and NTE mechanisms depend on LET, and thereby enhances our understanding of space radiation-induced cancer risks. The results suggest that LET values around 100 keV/µm correspond to maximal values for both TE and NTE processes. However, the shapes of the LET dependences for TE and NTE were different, with NTE increasing more rapidly with LET over 2-22 keV/µm, compared with TE. These findings provide a rationale for further research into how NTE phenomena depend on microscopic energy deposition patterns, and why these dependences may differ from those for TE. Our model also provides information on dose response shapes, which can prove useful for assessing additivity vs non-additivity of effects from space-relevant radiation mixtures. Additivity is expected at low doses, below the dose range where NTE saturation occurs. Doses encountered in space during a prolonged interplanetary mission are likely to overlap the range of where additivity may change to sub-additivity. References 7. Shuryak I, Fornace AJ, Datta K et al. Scaling Human Cancer Risks from Low LET to High LET when Dose-Effect Relationships are Complex. Radiat Res 2017;187:476–82. 8. Shuryak I, Sachs RK, Brenner DJ. Biophysical Models of Radiation Bystander Effects: 1. Spatial Effects in Three-Dimensional Tissues. Radiat Res 2007;168:741–9. 9. Shuryak I. Quantitative modeling of responses to chronic ionizing radiation exposure using targeted and non-targeted effects. PLoS One 2017;12:e0176476. 10. Shuryak I, Brenner DJ. Mechanistic modeling predicts no significant dose rate effect on heavy-ion carcinogenesis at dose rates relevant for space exploration. Radiat Prot Dosimetry 2019;183:203–12.
Bibliography Type:	Description: (Last Updated: 06/28/2023)
Articles in Peer-reviewed Journals	Shuryak I, Brenner DJ. "Mechanistic modeling predicts no significant dose rate effect on heavy-ion carcinogenesis at dose rates relevant for space exploration." Radiation Protection Dosimetry. 2019 May 1;183(1-2):203-12. https://doi.org/10.1093/rpd/ncy223 ; PubMed PMID: 30535099 , May-2019