Fiscal Year:	FY 2020	**Task Last Updated:**	FY 09/07/2020
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
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No. of PhD Candidates:		**No. of Master' Degrees:**	
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No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Key Personnel Changes/Previous PI:	n/a		
COI Name (Institution):	Hei, Tom Ph.D. (Columbia University Center for Radiological Research)		
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Task Description:	The main goal of the current project is state of the art mechanistically-motivated modeling of experimental data from NASA 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 (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 1.8 million new cancer cases and over 606,500 cancer-related deaths are predicted to occur in the US 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:	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 and continue to refine them (Shuryak et al., 2017; Shuryak and Brenner, 2019). Here we apply our modeling approach to recently updated and expanded data obtained by our collaborators from Georgetown University at the NASA Space Radiation Laboratory (NSRL). This is a detailed data set on APC(1638N/+) mouse tumorigenesis induced by space-relevant doses of protons, 4He, 12C, 16O, 28Si, or 56Fe ions, or gamma rays. A customized WNB distribution was used to model the data variability, which exhibited either under- or over-dispersion relative to the Poisson distribution, depending on radiation dose and type. This data set and modeling approach allowed detailed quantification of dose-response shapes, NTE and TE model parameters, and radiation quality metrics (relative biological effectiveness, RBE, and radiation effects ratio, RER, relative to gamma rays) for each radiation type. The best-fit dose response for each radiation type was a smooth function, asymptotically linear at very low doses where NTE dominate and also asymptotically linear at high doses where TE dominate, but concave at intermediate doses. Both NTE and TE parameters increased with radiation linear energy transfer (LET) from gamma rays to Si ions, with evidence for saturation/decrease at very high LET >70 keV/µm. RBE and RER were asymptotically the same at very low and very high doses, but RBE exceeded RER by up to several-fold in the intermediate space-relevant dose range. The proposed modeling approach can enhance current knowledge about quantification of health risks from space radiation. RBE and RER can be used to scale gamma ray-induced human colon cancer risks to space radiations, generating dose-dependent risk estimates for protons and each type of heavy ions for astronauts. Bibliography (publications reported in previous years): Shuryak, I., Brenner, D.J., 2019. Mechanistic modeling predicts no significant dose rate effect on heavy-ion carcinogenesis at dose rates relevant for space exploration. Radiat. Prot. Dosimetry 183, 203–212. 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.
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